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(54) Title: IMIDAZO[1,2- α]PYRIDINE DERIVATIVES AS MODULATORS OF THE 5-HT_{2A} SEROTONIN RECEPTOR USEFUL FOR THE TREATMENT OF DISORDERS RELATED THERETO

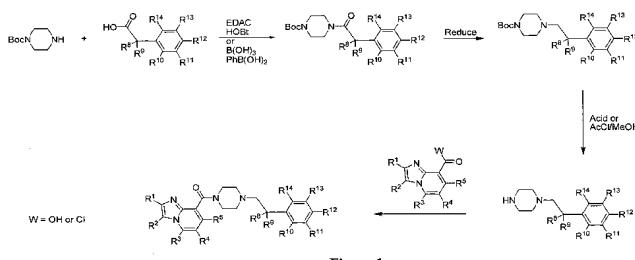
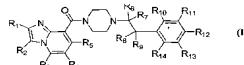


Figure 1



(57) Abstract: rmidazo[1,2- α]pyridine derivatives of Formula (Ia) and pharmaceutical compositions thereof that modulate the activity of the 5-HT_{2A} serotonin receptor. Compounds and pharmaceutical compositions thereof are directed to methods useful in the treatment of insomnia, dyssomnia, parasomnia and related sleep disorders, platelet aggregation, coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, thrombosis, asthma or symptoms thereof, agitation or symptoms thereof, behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorders, psychosis, acute schizophrenia, chronic schizophrenia, NOS schizophrenia and related disorders, diabetic- related disorders, progressive multifocal leukoencephalopathy and the like. The present invention also relates to methods for the treatment of 5-HT_{2A} serotonin receptor mediated disorders in combination with other pharmaceutical agents administered separately or together.

**IMIDAZO[1,2-*a*]PYRIDINE DERIVATIVES AS MODULATORS OF THE 5-HT_{2A}
SEROTONIN RECEPTOR USEFUL FOR THE TREATMENT OF DISORDERS
RELATED THERETO**

5

FIELD OF THE INVENTION

The present invention relates to certain imidazo[1,2-*a*]pyridine derivatives of Formula (Ia) and pharmaceutical compositions thereof that modulate the activity of the 5-HT_{2A} serotonin receptor. Compounds of Formula (Ia) and pharmaceutical compositions thereof are directed to methods useful in the treatment of insomnia and related sleep disorders, platelet aggregation, 10 coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, thrombosis, asthma or symptoms thereof, agitation or symptoms thereof, behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorders, psychosis, acute schizophrenia, chronic schizophrenia, NOS schizophrenia and related disorders, diabetic-related disorders, 15 progressive multifocal leukoencephalopathy and the like.

The present invention also relates to methods for the treatment of 5-HT_{2A} serotonin receptor mediated disorders in combination with other pharmaceutical agents administered separately or together.

20

BACKGROUND OF THE INVENTION

Serotonin receptors

Receptors for serotonin (5-hydroxytryptamine, 5-HT) are an important class of G protein coupled receptors. Serotonin is thought to play a role in processes related to learning and memory, sleep, thermoregulation, mood, motor activity, pain, sexual and aggressive behaviors, appetite, 25 neurodegenerative regulation and biological rhythms. Not surprisingly, serotonin is linked to pathophysiological conditions such as anxiety, depression, obsessive compulsive disorders, schizophrenia, suicide, autism, migraine, emesis, alcoholism and neurodegenerative disorders. With respect to anti-psychotic treatment approaches focused on the serotonin receptors, these types of therapeutics can generally be divided into two classes, the "typical" and the "atypical." Both 30 have anti-psychotic effects, but the typicals also include concomitant motor-related side effects (extra pyramidal syndromes, *e.g.*, lip-smacking, tongue darting, locomotor movement, *etc.*) Such side effects are thought to be associated with the compounds interacting with other receptors, such as the human dopamine D₂ receptor in the nigro-striatal pathway. Therefore, an atypical treatment is preferred. Haloperidol is considered a typical anti-psychotic and clozapine is considered an 35 atypical anti-psychotic.

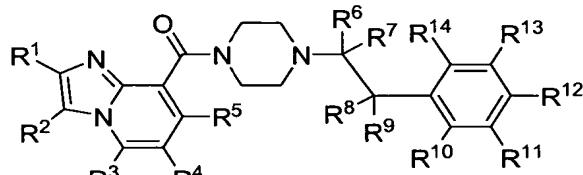
Serotonin receptors are divided into seven subfamilies, referred to as 5-HT₁ through 5-HT₇, inclusive. These subfamilies are further divided into subtypes. For example, the 5-HT₂

subfamily is divided into three receptor subtypes: 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}. The human 5-HT_{2C} receptor was first isolated and cloned in 1987 and the human 5-HT_{2A} receptor was first isolated and cloned in 1990.

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SUMMARY OF THE INVENTION

One aspect of the present invention encompasses certain imidazo[1,2-*a*]pyridine derivatives selected from compounds as shown in Formula (Ia):



(Ia)

10

and pharmaceutically acceptable salts, solvates and hydrates thereof;

wherein:

R¹ and R² are each independently selected from the group consisting of H, C₁-C₆ acyl, C₁-C₆ acyloxy, C₁-C₆ alkoxy, C₁-C₆ alkoxycarbonylamino, C₁-C₆ alkyl, C₁-C₆ alkylamino, C₂-C₈ dialkylamino, C₁-C₆ alkylcarboxamide, C₁-C₆ alkylsulfonamide, C₁-C₆ alkylsulfinyl, C₁-C₆ alkylsulfonyl, C₁-C₆ alkylureyl, amino, aryl, aryl-C₁-C₄-alkylenyl, carbo-C₁-C₆-alkoxy, carboxamide, carboxy, cyano, C₃-C₇ cycloalkyl, C₂-C₆ dialkylcarboxamide, C₁-C₆ haloalkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkylsulfinyl, C₁-C₆ haloalkylsulfonyl, halogen, heteroaryl, heterocycl, hydroxyl, nitro and sulfonamide;

15

R³, R⁴ and R⁵ are each independently selected from the group consisting of H, C₁-C₆ acyl, C₁-C₆ acyloxy, C₁-C₆ alkoxy, C₁-C₆ alkoxycarbonylamino, C₁-C₆ alkyl, C₁-C₆ alkylamino, C₂-C₈ dialkylamino, C₁-C₆ alkylcarboxamide, C₁-C₆ alkylsulfonamide, C₁-C₆ alkylsulfinyl, C₁-C₆ alkylsulfonyl, C₁-C₆ alkylureyl, amino, aryl, aryl-C₁-C₄-alkylenyl, carbo-C₁-C₆-alkoxy, carboxamide, carboxy, cyano, C₃-C₇ cycloalkyl, C₂-C₆ dialkylcarboxamide, C₁-C₆ haloalkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkylsulfinyl, C₁-C₆ haloalkylsulfonyl, halogen, heteroaryl, heterocycl, hydroxyl, nitro and sulfonamide;

20

R⁶, R⁷ are each independently selected from the group consisting of H, C₁-C₆ acyl, C₁-C₃ alkyl, aryl, carboxamide, carboxy, C₃-C₇ cycloalkyl, C₁-C₆ haloalkyl, heteroaryl and heterocycl;

25

R⁸ and R⁹ are each independently selected from the group consisting of H, C₁-C₆ acyl, C₁-C₃ alkyl, aryl, carboxamide, C₁-C₃ alkoxy, carboxy, cyano, C₃-C₇ cycloalkyl, C₁-C₃ haloalkyl, halogen and hydroxyl; or

R⁸ and R⁹ taken together form oxo; or

R⁸ and R⁹ together with the atom to which they are both bonded form a C₃-C₇ cycloalkyl ring; and

R¹⁰, R¹¹, R¹², R¹³ and R¹⁴ are each independently selected from the group consisting of H, C₁-C₆ acyl, C₁-C₆ acyloxy, C₁-C₆ alkoxy, C₁-C₆ alkoxycarbonylamino, C₁-C₆ alkyl, C₁-C₆ alkylamino, C₁-C₆ alkylcarboxamide, C₁-C₆ alkylsulfinyl, C₁-C₆ alkylsulfonamide, C₁-C₆ alkylsulfonyl, C₁-C₆ alkylureyl, amino, carbo-C₁-C₆ alkoxy, carboxamide, carboxy, cyano, C₃-C₆ cycloalkyl, C₃-C₇ cycloalkylcarbonyl, C₂-C₈ dialkylamino, C₂-C₆ dialkylcarboxamide, C₁-C₆ haloalkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkylsulfinyl, C₁-C₆ haloalkylsulfonyl, halogen, heteroaryl, heterocyclyl, hydroxyl, nitro, phenyl, sulfonamide and sulfonic acid; wherein said phenyl group is optionally substituted with 1, 2 or 3 halogens.

One aspect of the present invention pertains to pharmaceutical compositions comprising 10 a compound of the present invention and a pharmaceutically acceptable carrier.

One aspect of the present invention pertains to methods for treating 5-HT_{2A} mediated disorders in an individual, comprising administering to said individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

15 One aspect of the present invention pertains to methods for treating 5-HT_{2A} mediated disorders selected from the group consisting of coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke and atrial fibrillation in an individual, comprising administering to said individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

20 One aspect of the present invention pertains to methods for treating sleep disorders in an individual, comprising administering to said individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating dyssomnias.

25 One aspect of the present invention pertains to methods for treating insomnia.

One aspect of the present invention pertains to methods for treating parasomnias.

One aspect of the present invention pertains to methods for increasing slow wave sleep in an individual, comprising administering to said individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

30 One aspect of the present invention pertains to methods for improving sleep consolidation in an individual, comprising administering to said individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

35 One aspect of the present invention pertains to methods for improving sleep maintenance in an individual, comprising administering to said individual in need thereof a

therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

5 One aspect of the present invention pertains to methods for treating conditions associated with platelet aggregation in an individual, comprising administering to said individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

10 One aspect of the present invention pertains to methods for reducing the risk of blood clot formation in an angioplasty or coronary bypass surgery individual, comprising administering to said individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for reducing the risk of blood clot formation in an individual, comprising administering to said individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

15 One aspect of the present invention pertains to methods for reducing the risk of blood clot formation in an individual suffering from atrial fibrillation, comprising administering to said individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

20 One aspect of the present invention pertains to methods for treating diabetic-related disorders in an individual, comprising administering to said individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

25 One aspect of the present invention pertains to methods for treating progressive multifocal leukoencephalopathy in an individual, comprising administering to said individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

30 One aspect of the present invention pertains to methods for treating hypertension in an individual, comprising administering to said individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating pain in an individual, comprising administering to said individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

35 One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the treatment of a sleep disorder.

One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the treatment of a dyssomnia.

One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the treatment of insomnia.

5 One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the treatment of a parasomnia.

One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for increasing slow wave sleep.

10 One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for improving sleep consolidation.

One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for improving sleep maintenance.

One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the treatment of a 5-HT_{2A} mediated disorder.

15 One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the treatment of coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke or atrial fibrillation.

20 One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the treatment of a condition associated with platelet aggregation.

One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the reduction of the risk of blood clot formation in an angioplasty or coronary bypass surgery individual.

25 One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the reduction of the risk of blood clot formation in an individual.

One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the reduction of the risk of blood clot formation in an individual suffering from atrial fibrillation.

30 One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the treatment of a diabetic-related disorder.

One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the treatment of progressive multifocal leukoencephalopathy.

35 One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the treatment of hypertension.

One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the treatment of pain.

One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of the human or animal body by therapy.

5 One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of the human or animal body by surgery.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of a 5-HT_{2A} mediated disorder.

10 One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke or atrial fibrillation.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of a sleep disorder.

15 One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of a dyssomnia.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of insomnia.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of a parasomnia.

20 One aspect of the present invention pertains to compounds of the present invention for use in a method for increasing slow wave sleep.

One aspect of the present invention pertains to compounds of the present invention for use in a method for improving sleep consolidation.

25 One aspect of the present invention pertains to compounds of the present invention for use in a method for improving sleep maintenance.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of a condition associated with platelet aggregation.

30 One aspect of the present invention pertains to compounds of the present invention for use in a method of reducing the risk of blood clot formation in an angioplasty or coronary bypass surgery individual.

One aspect of the present invention pertains to compounds of the present invention for use in a method of reducing the risk of blood clot formation in an individual.

35 One aspect of the present invention pertains to compounds of the present invention for use in a method of reducing the risk of blood clot formation in an individual suffering from atrial fibrillation.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of a diabetic-related disorder.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of progressive multifocal leukoencephalopathy.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of hypertension.

5 One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of pain.

One aspect of the present invention pertains to processes for preparing a composition comprising admixing a compound of the present invention and a pharmaceutically acceptable carrier.

10 These and other aspects of the invention disclosed herein will be set forth in greater detail as the patent disclosure proceeds.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a general synthetic scheme for preparation of compounds of Formula 15 (Ia). Boc-piperazine is coupled with a phenylacetic acid derivative in the presence of a coupling agent. The resulting amide is reduced and the Boc protecting group is removed. The final step is coupling with an imidazopyridine carboxylic acid derivative.

20 Figure 2 shows a second general synthetic scheme for preparation of compounds of Formula (Ia). Here the Boc-piperazine is coupled with a phenethyl halide derivative, followed by deprotection and finally coupling with an imidazopyridine carboxylic acid derivative.

25 Figure 3 shows synthetic schemes for preparation of certain imidazo[1,2-a]pyridines. The first synthesis involves the reaction between an acetaldehyde derivative and a 2-aminonicotinic acid derivative to produce an imidazo[1,2-a]pyridine-8-carboxylic acid, which can then be chlorinated to form the acid chloride. Alternatively 2-aminonicotinic acids are methylated with TMS-diazomethane and reacted with disubstituted carbonyl compounds to produce certain imidazo[1,2-a]pyridine-8-carboxylic acid methyl esters, which can be subsequently demethylated.

Halogenation at the 3-position of an imidazo[1,2-a]pyridine-8-carboxylic acid derivative, by treatment with a halogenating agent, is also shown.

30 Figure 4 shows halogenation of a compound of Formula (Ia) with a halogenating agent and cyanation of a compound of Formula (Ia) with dicyanozinc.

Figure 5 shows a third route for preparing compounds of Formula (Ia) wherein the imidazo[1,2-a]pyridine derivative is coupled first to the Boc-piperidine. After deprotection the final step is coupling with a phenethyl halide derivative.

35 Figure 6 shows the efficacy of compound 18 in the attenuation of DOI-induced hypolocomotion in rats.

Figure 7 shows the efficacy of compound in 19 the attenuation of DOI-induced hypolocomotion in rats.

DETAILED DESCRIPTION OF THE INVENTION

5 DEFINITIONS

For clarity and consistency, the following definitions will be used throughout this patent document.

The term “**agonists**” is intended to mean moieties that interact and activate the receptor, such as the 5-HT_{2A} serotonin receptor and initiate a physiological or pharmacological response characteristic of that receptor. For example, when moieties activate the intracellular response upon binding to the receptor, or enhance GTP binding to membranes.

The term “**antagonists**” is intended to mean moieties that competitively bind to the receptor at the same site as agonists (for example, the endogenous ligand), but which do not activate the intracellular response initiated by the active form of the receptor and can thereby inhibit the intracellular responses by agonists or partial agonists. Antagonists do not diminish the baseline intracellular response in the absence of an agonist or partial agonist.

The term “**contact or contacting**” is intended to mean bringing the indicated moieties together, whether in an *in vitro* system or an *in vivo* system. Thus, “contacting” a 5-HT_{2A} serotonin receptor with a compound of the invention includes the administration of a compound of the present invention to an individual, preferably a human, having a 5-HT_{2A} serotonin receptor, as well as, for example, introducing a compound of the invention into a sample containing a cellular or more purified preparation containing a 5-HT_{2A} serotonin receptor.

The term “**in need of treatment**” and the term “**in need thereof**” when referring to treatment are used interchangeably to mean a judgment made by a caregiver (*e.g.* physician, nurse, nurse practitioner, *etc.* in the case of humans; veterinarian in the case of animals, including non-human mammals) that an individual or animal requires or will benefit from treatment. This judgment is made based on a variety of factors that are in the realm of a caregiver’s expertise, but that includes the knowledge that the individual or animal is ill, or will become ill, as the result of a disease, condition or disorder that is treatable by the compounds of the invention. Accordingly, the compounds of the invention can be used in a protective or preventive manner; or compounds of the invention can be used to alleviate, inhibit or ameliorate the disease, condition or disorder.

The term “**individual**” is intended to mean any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates and most preferably humans.

The term “**inverse agonists**” is intended to mean moieties that bind to the endogenous form of the receptor or to the constitutively activated form of the receptor and which inhibit the

baseline intracellular response initiated by the active form of the receptor below the normal base level of activity which is observed in the absence of agonists or partial agonists, or decrease GTP binding to membranes. Preferably, the baseline intracellular response is inhibited in the presence of the inverse agonist by at least 30%, more preferably by at least 50% and most preferably by at least 5 75%, as compared with the baseline response in the absence of the inverse agonist.

The term "**modulate or modulating**" is intended to mean an increase or decrease in the amount, quality, response or effect of a particular activity, function or molecule.

The term "**pharmaceutical composition**" is intended to mean a composition comprising at least one active ingredient; including but not limited to, salts, solvates and hydrates of 10 compounds of the present invention; whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

The term "**therapeutically effective amount**" is intended to mean the amount of active 15 compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician or caregiver; or by an individual, which includes one or more of the following:

(1) Preventing the disease; for example, preventing a disease, condition or disorder in an 20 individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease,

(2) Inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (*i.e.*, arresting further development of the pathology and/or 25 symptomatology) and

(3) Ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (*i.e.*, reversing the pathology and/or symptomatology).

30 **CHEMICAL GROUP, MOIETY OR RADICAL**

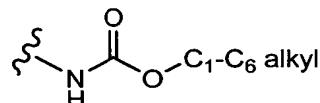
The term "**C₁-C₆ acyl**" is intended to mean a C₁-C₆ alkyl radical attached to the carbon of a carbonyl group wherein the definition of alkyl has the same definition as described herein; some examples include, but are not limited to, acetyl, propionyl, *n*-butanoyl, *sec*-butanoyl, pivaloyl, pentanoyl and the like.

35 The term "**C₁-C₆ acyloxy**" is intended to mean an acyl radical attached to an oxygen atom wherein acyl has the same definition has described herein; some embodiments are when acyloxy is C₁-C₅ acyloxy, some embodiments are when acyloxy is C₁-C₆ acyloxy. Some

examples include, but are not limited to, acyloxy, propionyloxy, butanoyloxy, *iso*-butanoyloxy, pentanoyloxy, hexanoyloxy and the like.

The term “C₁-C₆ alkoxy” is intended to mean a C₁-C₆ alkyl radical, as defined herein, attached directly to an oxygen atom, some embodiments are 1 to 5 carbons, some embodiments are 1 to 4 carbons, some embodiments are 1 to 3 carbons and some embodiments are 1 or 2 carbons. Examples include methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *t*-butoxy, *iso*-butoxy, *sec*-butoxy and the like.

The term “C₁-C₆ alkoxy carbonylamino” is intended to mean a single C₁-C₆ alkoxy group attached to the carbon of an amide group wherein alkoxy has the same definition as found herein. The alkoxy carbonylamino group may be represented by the following:



The term “C₁-C₆ alkyl” is intended to mean a straight or branched carbon radical containing 1 to 6 carbons, some embodiments are 1 to 5 carbons, some embodiments are 1 to 4 carbons, some embodiments are 1 to 3 carbons and some embodiments are 1 or 2 carbons.

Examples of an alkyl include, but not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *t*-butyl, pentyl, *iso*-pentyl, *t*-pentyl, *neo*-pentyl, 1-methylbutyl [*i.e.*, -CH(CH₃)CH₂CH₂CH₃], 2-methylbutyl [*i.e.*, -CH₂CH(CH₃)CH₂CH₃], *n*-hexyl and the like.

The term “C₁-C₆ alkylcarboxamido” or “C₁-C₆ alkylcarboxamide” is intended to mean a single C₁-C₆ alkyl group attached to either the carbon or the nitrogen of an amide group, wherein alkyl has the same definition as found herein. The C₁-C₆ alkylcarboxamido group may be represented by the following:



Examples include, but are not limited to, *N*-methylcarboxamide, *N*-ethylcarboxamide, *N-n*-propylcarboxamide, *N*-*iso*-propylcarboxamide, *N*-*n*-butylcarboxamide, *N*-*sec*-butylcarboxamide, *N*-*iso*-butylcarboxamide, *N*-*t*-butylcarboxamide and the like.

The term “C₁-C₆ alkylsulfinyl” is intended to mean a C₁-C₆ alkyl radical attached to the sulfur of a sulfoxide radical having the formula: -S(O)- wherein the alkyl radical has the same definition as described herein. Examples include, but are not limited to, methylsulfinyl, ethylsulfinyl, *n*-propylsulfinyl, *iso*-propylsulfinyl, *n*-butylsulfinyl, *sec*-butylsulfinyl, *iso*-butylsulfinyl, *t*-butylsulfinyl and the like.

The term “C₁-C₆ alkylsulfonamide” is intended to mean the groups shown below:



wherein C₁-C₆ alkyl has the same definition as described herein.

The term “C₁-C₆ alkylsulfonyl” is intended to mean a C₁-C₆ alkyl radical attached to the sulfur of a sulfone radical having the formula: -S(O)₂- wherein the alkyl radical has the same definition as described herein. Examples include, but are not limited to, methylsulfonyl, ethylsulfonyl, *n*-propylsulfonyl, *iso*-propylsulfonyl, *n*-butylsulfonyl, *sec*-butylsulfonyl, *iso*-butylsulfonyl, *t*-butylsulfonyl and the like.

The term “C₁-C₆ alkylureyl” is intended to mean the group of the formula: -NC(O)N- wherein one or both of the nitrogens are substituted with the same or different C₁-C₆ alkyl group 10 wherein alkyl has the same definition as described herein. Examples of an alkylureyl include, but are not limited to, CH₃NHC(O)NH-, NH₂C(O)NCH₃-, (CH₃)₂NC(O)NH-, (CH₃)₂NC(O)NCH₃-, CH₃CH₂NHC(O)NH-, CH₃CH₂NHC(O)NCH₃- and the like.

The term “amino” is intended to mean the group -NH₂.

The term “C₁-C₆ alkylamino” is intended to mean one alkyl radical attached to a -NH- radical wherein the alkyl radical has the same meaning as described herein. Some examples 15 include, but are not limited to, methylamino, ethylamino, *n*-propylamino, *iso*-propylamino, *n*-butylamino, *sec*-butylamino, *iso*-butylamino, *t*-butylamino and the like. Some embodiments are “C₁-C₂ alkylamino.”

The term “aryl” is intended to mean an aromatic ring radical containing 6 to 10 ring 20 carbons. Examples include phenyl and naphthyl.

The term “aryl-C₁-C₄-alkylenyl” is intended to mean a C₁-C₄ alkylene group bonded to an aryl group, each as defined herein. In some embodiments aryl-C₁-C₄-alkylenyl refers to, for example, benzyl (-CH₂-phenyl), phenylethyl (-CH₂CH₂-phenyl) and the like

The term “carbo-C₁-C₆-alkoxy” is intended to mean a C₁-C₆ alkyl ester of a carboxylic acid, wherein the alkyl group is as defined herein. Examples include, but are not limited to, 25 carbomethoxy [-C(=O)OCH₃], carboethoxy, carbopropoxy, carboisopropoxy, carbobutoxy, carbo-*sec*-butoxy, carbo-*iso*-butoxy, carbo-*t*-butoxy, carbo-*n*-pentoxy, carbo-*iso*-pentoxy, carbo-*t*-pentoxy, carbo-*neo*-pentoxy, carbo-*n*-hexyloxy and the like.

The term “carboxamide” is intended to mean the group -CONH₂.

The term “carboxy” or “carboxyl” is intended to mean the group -CO₂H; also referred 30 to as a carboxylic acid group.

The term “cyano” is intended to mean the group -CN.

The term “C₃-C₇ cycloalkyl” is intended to mean a saturated ring radical containing 3 to 7 carbons; some embodiments contain 3 to 6 carbons; some embodiments contain 3 to 5 35 carbons; some embodiments contain 5 to 7 carbons; some embodiments contain 3 to 4 carbons. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like.

The term “C₃-C₇ cycloalkylcarbonyl” is intended to mean a C₃-C₇ cycloalkyl attached to the carbon of a carbonyl group wherein C₃-C₇ cycloalkyl has the same definition as described herein. Examples include cyclopropanecarbonyl, cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, cycloheptylcarbonyl and the like.

5 The term “C₂-C₈ dialkylamino” is intended to mean an amino substituted with two of the same or different C₁-C₄ alkyl radicals wherein alkyl radical has the same definition as described herein. Some examples include, but are not limited to, dimethylamino, methylethylamino, diethylamino, methylpropylamino, methylisopropylamino, ethylpropylamino, ethylisopropylamino, dipropylamino, propylisopropylamino and the like.

10 Some embodiments are “C₂-C₄ dialkylamino.”

The term “C₂-C₆ dialkylcarboxamido” or “C₂-C₆ dialkylcarboxamide” is intended to mean two alkyl radicals, that are the same or different, attached to an amide group, wherein alkyl has the same definition as described herein. A C₂-C₆ dialkylcarboxamido may be represented by the following groups:



15

wherein C₁-C₃ has the same definition as described herein. Examples of a dialkylcarboxamide include, but are not limited to, N,N-dimethylcarboxamide, N-methyl-N-ethylcarboxamide, N,N-diethylcarboxamide, N-methyl-N-isopropylcarboxamide and the like.

20 The term “C₁-C₆ haloalkoxy” is intended to mean a C₁-C₆ haloalkyl, as defined herein, which is directly attached to an oxygen atom. Examples include, but are not limited to, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, pentafluoroethoxy and the like.

25 The term “C₁-C₆ haloalkyl” is intended to mean an C₁-C₆ alkyl group, defined herein, wherein the alkyl is substituted with one halogen up to fully substituted and a fully substituted C₁-C₆ haloalkyl can be represented by the formula C_nL_{2n+1} wherein L is a halogen and “n” is 1, 2, 3, 4, 5 or 6; when more than one halogen is present then they may be the same or different and selected from the group consisting of F, Cl, Br and I, preferably F, some embodiments are 1 to 5 carbons, some embodiments are 1 to 4 carbons, some embodiments are 1 to 3 carbons and some embodiments are 1 or 2 carbons. Examples of haloalkyl groups include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, chlorodifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl and the like.

30 The term “C₁-C₆ haloalkylsulfinyl” is intended to mean a C₁-C₆ haloalkyl radical attached to the sulfur atom of a sulfoxide group having the formula: -S(O)- wherein the haloalkyl radical has the same definition as described herein. Examples include, but are not limited to, trifluoromethylsulfinyl, 2,2,2-trifluoroethylsulfinyl, 2,2-difluoroethylsulfinyl and the like.

The term "**C₁-C₆ haloalkylsulfonyl**" is intended to mean a C₁-C₆ haloalkyl radical attached to the sulfur atom of a sulfone group having the formula: -S(O)₂- wherein haloalkyl has the same definition as described herein. Examples include, but are not limited to, trifluoromethylsulfonyl, 2,2,2-trifluoroethylsulfonyl, 2,2-difluoroethylsulfonyl and the like.

5 The term "**halogen**" or "**halo**" is intended to mean to a fluoro, chloro, bromo or iodo group.

The term "**heteroaryl**" is intended to mean an aromatic ring system containing 5 to 14 aromatic ring atoms that may be a single ring, two fused rings or three fused rings wherein at least one aromatic ring atom is a heteroatom selected from, for example, but not limited to, the 10 group consisting of O, S and N wherein the N can be optionally substituted with H, C₁-C₄ acyl or C₁-C₄ alkyl. Some embodiments contain 5 to 6 ring atoms for example furanyl, thienyl, pyrrolyl, imidazolyl, oxazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl and triazinyl and the like. Some embodiments contain 8 to 14 ring atoms for example quinolizinyl, quinolinyl, 15 isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxaliny, triazinyl, indolyl, isoindolyl, indazolyl, indolizinyl, purinyl, naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, benzoxazolyl, benzothiazolyl, 1H-benzimidazolyl, imidazopyridinyl, benzothienyl, benzofuranyl, and isobenzofuran and the like

The term "**heterocyclic**" or "**heterocyclyl**" is intended to mean a non-aromatic carbon 20 ring containing 3 to 8 ring atoms wherein one, two or three ring carbons are replaced by a heteroatom selected from, for example, the group consisting of O, S, S(=O), S(=O)₂ and NH, wherein the N is optionally substituted as described herein. In some embodiments, the nitrogen is optionally substituted with C₁-C₄ acyl or C₁-C₄ alkyl and ring carbon atoms are optionally substituted with oxo or a thioxo thus forming a carbonyl or thiocarbonyl group. The 25 heterocyclic group can be attached/bonded to any available ring atom, for example, ring carbon, ring nitrogen and the like. In some embodiments the heterocyclic group is a 3-, 4-, 5-, 6- or 7-membered ring. Examples of a heterocyclic group include, but are not limited to, aziridin-1-yl, aziridin-2-yl, azetidin-1-yl, azetidin-2-yl, azetidin-3-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, morpholin-2-yl, morpholin-3-yl, morpholin-4-yl, piperzin-1-yl, piperzin-2-yl, piperzin-3-yl, piperzin-4-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, [1,3]-dioxolan-30 2-yl, thiomorpholin-C₄-yl, [1,4]oxazepan-4-yl, 1,1-dioxothiomorpholin-4-yl, azepan-1-yl, azepan-2-yl, azepan-3-yl, azepan-4-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl and the like.

The term "**hydroxyl**" is intended to mean the group -OH.

The term "**nitro**" is intended to mean the group -NO₂.

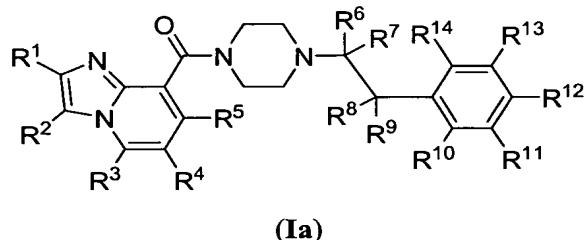
35 The term "**oxo**" is intended to mean the substituent =O, accordingly, as a result, when a carbon is substituted by an "oxo" group the new group resulting from the carbon and oxo together is a carbonyl group.

The term “**sulfonamide**” is intended to mean the group $\text{-SO}_2\text{NH}_2$.

The term “**sulfonic acid**” is intended to mean the group $\text{-SO}_3\text{H}$.

COMPOUNDS OF THE INVENTION:

5 One aspect of the present invention pertains to certain compounds as shown in Formula (Ia):



and pharmaceutically acceptable salts, solvates and hydrates thereof;

10 wherein:

$\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5, \text{R}^6, \text{R}^7, \text{R}^8, \text{R}^9, \text{R}^{10}, \text{R}^{11}, \text{R}^{12}, \text{R}^{13}$ and R^{14} have the same definitions as described herein, *supra* and *infra*.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single 15 embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination. All combinations of the embodiments pertaining to the chemical groups represented by the variables (e.g., $\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5, \text{R}^6, \text{R}^7, \text{R}^8, \text{R}^9, \text{R}^{10}, \text{R}^{11}, \text{R}^{12}, \text{R}^{13}$ and R^{14}) contained within the generic chemical formulae described herein, for example, (Ia, Ic and Ie) 20 are specifically embraced by the present invention just as if each and every combination was individually explicitly recited, to the extent that such combinations embrace compounds that result in stable compounds (*i.e.*, compounds that can be isolated, characterized and tested for biological activity). In addition, all subcombinations of the chemical groups listed in the embodiments describing such variables, as well as all subcombinations of uses and medical 25 indications described herein, are also specifically embraced by the present invention just as if each and every subcombination of chemical groups and subcombination of uses and medical indications was individually and explicitly recited herein.

As used herein, “substituted” indicates that at least one hydrogen atom of the chemical group is replaced by a non-hydrogen substituent or group, the non-hydrogen substituent or 30 group can be monovalent or divalent. When the substituent or group is divalent, then it is understood that this group is further substituted with another substituent or group. When a chemical group herein is “substituted” it may have up to the full valance of substitution; for example, a methyl group can be substituted by 1, 2, or 3 substituents, a methylene group can be substituted by 1 or 2 substituents, a phenyl group can be substituted by 1, 2, 3, 4, or 5

substituents, a naphthyl group can be substituted by 1, 2, 3, 4, 5, 6, or 7 substituents and the like. Likewise, “substituted with one or more substituents” refers to the substitution of a group with one substituent up to the total number of substituents physically allowed by the group. Further, when a group is substituted with more than one group they can be identical or they can be
5 different.

Compounds of the invention can also include tautomeric forms, such as keto-enol tautomers and the like. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution. It is understood that the various tautomeric forms are within the scope of the compounds of the present invention.

10 Compounds of the invention can also include all isotopes of atoms occurring in the intermediates and/or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include deuterium and tritium.

15 It is understood and appreciated that compounds of Formula (**Ia**) and formulae related thereto may have one or more chiral centers and therefore can exist as enantiomers and/or diastereomers. The invention is understood to extend to and embrace all such enantiomers, diastereomers and mixtures thereof, including but not limited to racemates. It is understood that compounds of Formula (**Ia**) and formulae used throughout this disclosure are intended to represent all individual enantiomers and mixtures thereof, unless stated or shown otherwise.

20

The Groups R¹ and R²

In some embodiments, R¹ and R² are each independently selected from the group consisting of H, C₁-C₆ acyloxy, C₁-C₆ alkoxy, C₁-C₆ alkyl, C₁-C₆ alkylsulfonyl, aryl, aryl-C₁-C₄-alkylenyl, carbo-C₁-C₆ alkoxy, carboxy, cyano, C₃-C₇ cycloalkyl, C₁-C₆ haloalkoxy, C₁-C₆ haloalkyl, halogen, heteroaryl, heterocycl and hydroxyl.
25

In some embodiments, R¹ and R² are each independently selected from the group consisting of H, C₁-C₆ alkyl, aryl, cyano, C₁-C₆ haloalkyl and halogen.

In some embodiments, R¹ and R² are each independently selected from the group consisting of H, methyl, *t*-butyl, phenyl, cyano, trifluoromethyl, chloro and bromo.

30

In some embodiments, R¹ is H; and R² is cyano, chloro or bromo.

In some embodiments, wherein R¹ and R² are both H.

The Groups R³, R⁴ and R⁵

In some embodiments, wherein R³, R⁴ and R⁵ are each independently selected from the group consisting of H, C₁-C₆ alkoxy, C₁-C₆ alkyl, cyano, C₁-C₆ haloalkoxy, C₁-C₆ haloalkyl, halogen and hydroxyl.
35

In some embodiments, R³, R⁴ and R⁵ are each independently selected from the group consisting of H, C₁-C₆ alkyl, C₁-C₆ alkoxy and halogen.

In some embodiments, R³ and R⁵ are each independently selected from the group consisting of H, C₁-C₆ alkyl and C₁-C₆ alkoxy; and R⁴ is H.

5 In some embodiments, wherein R³, R⁴ and R⁵ are each independently selected from the group consisting of H, methyl, methoxy and bromo.

In some embodiments, R³, R⁴ and R⁵ are each H.

The Groups R⁶ and R⁷

10 In some embodiments, R⁶ and R⁷ are each independently selected from the group consisting of H and C₁-C₃ alkyl.

In some embodiments, wherein R⁶ and R⁷ are each independently selected from the group consisting of H and methyl.

In some embodiments, wherein R⁶ and R⁷ are both H.

15

The Groups R⁸ and R⁹

In some embodiments, R⁸ and R⁹ are each independently selected from the group consisting of H, C₁-C₃ alkyl, aryl, C₁-C₃ alkoxy, C₃-C₇ cycloalkyl, C₁-C₃ haloalkyl, halogen and hydroxyl; or

20 R⁸ and R⁹ taken together form oxo; or

R⁸ and R⁹ together with the atom to which they are both bonded form a C₃-C₇ cycloalkyl ring.

In some embodiments, R⁸ and R⁹ are each independently selected from the group consisting of H and halogen; or

25 R⁸ and R⁹ together form oxo.

In some embodiments, R⁸ and R⁹ are each independently selected from the group consisting of H and F; or

R⁸ and R⁹ together form oxo.

In some embodiments, R⁸ and R⁹ are both H.

30 In some embodiments, wherein R⁸ and R⁹ together form oxo.

The Groups R¹⁰, R¹¹, R¹², R¹³ and R¹⁴

In some embodiments, R¹⁰, R¹¹, R¹², R¹³ and R¹⁴ are each independently selected from the group consisting of H, C₁-C₆ acyloxy, C₁-C₆ alkoxy, C₁-C₆ alkyl, C₁-C₆ alkylamino, C₂-C₈ dialkylamino, C₁-C₆ alkylcarboxamide, C₁-C₆ alkylsulfonamide, C₁-C₆ alkylsulfonyl, amino, carboxamide, carboxy, cyano, C₃-C₆ cycloalkyl, C₂-C₆ dialkylcarboxamide, C₁-C₆ haloalkoxy,

C₁-C₆ haloalkyl, halogen, heteroaryl, heterocyclyl, hydroxyl, nitro, phenyl, sulfonamide and sulfonic acid; wherein said phenyl group is optionally substituted with 1, 2 or 3 halogens.

In some embodiments, R¹⁰, R¹¹, R¹², R¹³ and R¹⁴ are each independently selected from the group consisting of H, C₁-C₆ alkoxy, C₁-C₆ alkyl, C₂-C₈ dialkylamino, C₁-C₆

5 alkylsulfonamide, C₁-C₆ alkylsulfonyl, carboxamide, carboxy, cyano, C₃-C₆ cycloalkyl, C₁-C₆ haloalkoxy, C₁-C₆ haloalkyl, halogen, heteroaryl, heterocyclyl, hydroxyl, nitro, phenyl and sulfonic acid.

In some embodiments, R¹⁰, R¹¹, R¹², R¹³ and R¹⁴ are each independently selected from the group consisting of H, methyl, methoxy, dimethylamino, -NHSO₂CH₃, methylsulfonyl, 10 carboxamide, carboxy, cyano, cyclohexyl, fluoro, chloro, trifluoromethoxy, difluoromethoxy, trifluoromethyl, morpholin-4-yl, pyrrolidin-1-yl, thien-2-yl, hydroxyl, nitro, phenyl and sulfonic acid.

In some embodiments:

R¹⁰ and R¹⁴ are each independently selected from the group consisting of H, C₁-C₆ 15 alkoxy, carboxy, halogen, C₁-C₆ haloalkoxy and C₁-C₆ haloalkyl;

R¹¹ and R¹³ are each independently selected from the group consisting of H, C₁-C₆ alkyl, C₁-C₆ alkylsulfonamide, C₁-C₆ alkoxy, carboxamide, C₁-C₆ haloalkyl, halogen, hydroxyl and nitro; and

20 R¹² is selected from the group consisting of H, C₁-C₆ alkoxy, C₁-C₆ alkyl, C₂-C₈ dialkylamino, C₁-C₆ alkylsulfonamide, C₁-C₆ alkylsulfonyl, carboxamide, cyano, C₃-C₆ cycloalkyl, C₁-C₆ haloalkoxy, C₁-C₆ haloalkyl, halogen, heterocyclyl, heteroaryl, hydroxyl, nitro, phenyl and sulfonic acid.

In some embodiments:

R¹⁰ and R¹⁴ are each independently selected from the group consisting of H, methoxy, 25 carboxy, fluoro, chloro and trifluoromethyl;

R¹¹ and R¹³ are each independently selected from the group consisting of H, methyl, methoxy, -NHSO₂CH₃, fluoro, chloro, carboxamide, hydroxyl, trifluoromethyl and nitro; and

30 R¹² is selected from the group consisting of H, methyl, methoxy, dimethylamino, -NHSO₂CH₃, methylsulfonyl, carboxamide, cyano, cyclohexyl, fluoro, chloro, trifluoromethoxy, difluoromethoxy, trifluoromethyl, morpholin-4-yl, pyrrolidin-1-yl, thien-2-yl, hydroxyl, nitro, phenyl and sulfonic acid.

In some embodiments:

R¹⁰, R¹² and R¹⁴ are each independently selected from the group consisting of H and halogen; and

35 R¹¹ and R¹³ are both H.

In some embodiments:

R¹⁰, R¹² and R¹⁴ are each independently selected from the group consisting of H and F;
and

R¹¹ and R¹³ are both H.

In some embodiments:

5 R¹⁰ and R¹² are both F; and
R¹¹, R¹³ and R¹⁴ are each H.

Some Preferred Combinations:

In some embodiments:

10 R¹ and R² are each independently selected from the group consisting of H, C₁-C₆ alkyl,
aryl, cyano, C₁-C₆ haloalkyl and halogen;

R³, R⁴ and R⁵ are each independently selected from the group consisting of H, C₁-C₆
alkyl, C₁-C₆ alkoxy and halogen;

15 R⁶ and R⁷ are each independently selected from the group consisting of H and C₁-C₃
alkyl;

R⁸ and R⁹ are each independently selected from the group consisting of H and halogen;
or

R⁸ and R⁹ together form oxo; or

20 R⁸ and R⁹ together with the atom to which they are both bonded form a C₃-C₇ cycloalkyl
ring; and

R¹⁰, R¹¹, R¹², R¹³ and R¹⁴ are each independently selected from the group consisting of
H, C₁-C₆ alkoxy, C₁-C₆ alkyl, C₂-C₈ dialkylamino, C₁-C₆ alkylsulfonamide, C₁-C₆ alkylsulfonyl,
carboxamide, carboxy, cyano, C₃-C₆ cycloalkyl, C₁-C₆ haloalkoxy, C₁-C₆ haloalkyl, halogen,
heteroaryl, heterocycl, hydroxyl, nitro, phenyl and sulfonic acid.

25 In some embodiments:

R¹ is selected from the group consisting of H, C₁-C₆ alkyl, aryl and C₁-C₆ haloalkyl;

R² is selected from the group consisting of H, cyano and halogen;

R³ is selected from the group consisting of H and C₁-C₆ alkyl; and

R⁴ is H or halogen; or

30 R³ and R⁴ together with the atoms to which they are both bonded form a heterocyclic
ring;

R⁵ is selected from the group consisting of H, C₁-C₆ alkoxy and C₁-C₆ alkyl;

R⁶ and R⁷ are both H;

R⁸ and R⁹ are each independently selected from the group consisting of H and halogen;

35 or
R⁸ and R⁹ together form oxo; and

R^{10} , R^{11} , R^{12} , R^{13} and R^{14} are each independently selected from the group consisting of H, C₁-C₆ alkoxy, C₁-C₆ alkyl, C₂-C₈ dialkylamino, C₁-C₆ alkylsulfonamide, C₁-C₆ alkylsulfonyl, carboxamide, carboxy, cyano, C₃-C₆ cycloalkyl, C₁-C₆ haloalkoxy, C₁-C₆ haloalkyl, halogen, heteroaryl, heterocyclyl, hydroxyl, nitro, phenyl and sulfonic acid.

5 In some embodiments:

R^1 is selected from the group consisting of H, methyl, *t*-butyl, phenyl and trifluoromethyl;

R^2 is selected from the group consisting of H, cyano, chloro and bromo;

R^3 is selected from the group consisting of H and methyl;

10 R^4 is H or bromo;

R^5 is selected from the group consisting of H and methyl;

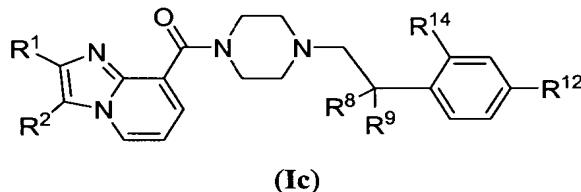
R^6 and R^7 are both H;

R^8 and R^9 are each independently selected from the group consisting of H and F; or

R^8 and R^9 together form oxo; and

15 R^{10} , R^{11} , R^{12} , R^{13} and R^{14} are each independently selected from the group consisting of H, methyl, methoxy, dimethylamino, -NHSO₂CH₃, methylsulfonyl, carboxamide, carboxy, cyano, cyclohexyl, fluoro, chloro, trifluoromethoxy, difluoromethoxy, trifluoromethyl, morpholin-4-yl, pyrrolidin-1-yl, thien-2-yl, hydroxyl, nitro, phenyl and sulfonic acid.

Some embodiments of the present invention pertain to compounds of Formula (Ic) and
20 pharmaceutically acceptable salts, solvates or hydrates thereof:



wherein:

R^1 is selected from the group consisting of H, C₁-C₆ alkyl, aryl and C₁-C₆ haloalkyl;

25 R^2 is selected from the group consisting of H, cyano and halogen;

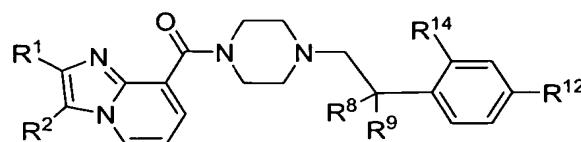
R^8 and R^9 are each independently selected from the group consisting of H and halogen;

or

R^8 and R^9 together form oxo; and

R^{12} and R^{14} are each independently selected from the group consisting of H and halogen.

30 Some embodiments of the present invention pertain to compounds of Formula (Ic) and pharmaceutically acceptable salts, solvates or hydrates thereof:



(Ic)

wherein:

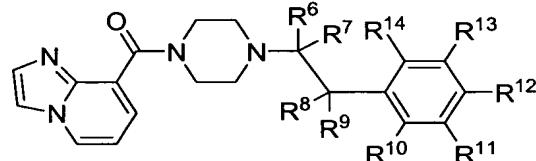
R¹ is selected from the group consisting of H, methyl, *t*-butyl, phenyl and trifluoromethyl;

5 R² is selected from the group consisting of H, cyano, chloro and bromo;

R⁸ and R⁹ are each independently selected from the group consisting of H and F; or
R⁸ and R⁹ together form oxo; and

10 R¹² and R¹⁴ are each independently selected from the group consisting of H, fluoro and chloro.

Some embodiments of the present invention pertain to compounds of Formula (Ie) and pharmaceutically acceptable salts, solvates or hydrates thereof:



(Ie)

wherein:

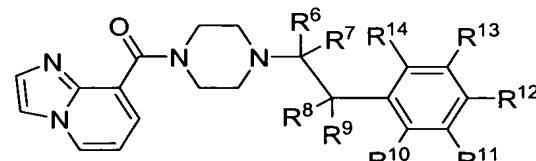
15 R⁶ and R⁷ are each independently selected from the group consisting of H and C₁-C₃ alkyl;

R⁸ and R⁹ are each independently selected from the group consisting of H and halogen; or

R⁸ and R⁹ together form oxo; and

20 R¹⁰, R¹¹, R¹², R¹³ and R¹⁴ are each independently selected from the group consisting of H, C₁-C₆ alkoxy, C₁-C₆ alkyl, C₂-C₈ dialkylamino, C₁-C₆ alkylsulfonamide, C₁-C₆ alkylsulfonyl, carboxamide, carboxy, cyano, C₃-C₆ cycloalkyl, C₁-C₆ haloalkoxy, C₁-C₆ haloalkyl, heteroaryl, halogen, heterocyclyl, hydroxyl, nitro, phenyl and sulfonic acid.

Some embodiments of the present invention pertain to compounds of Formula (Ie) and pharmaceutically acceptable salts, solvates or hydrates thereof:



(Ie)

wherein:

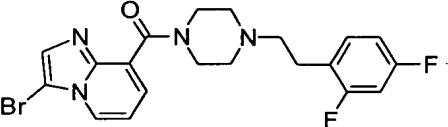
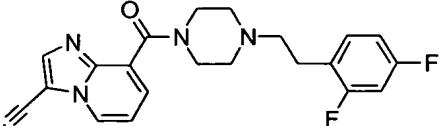
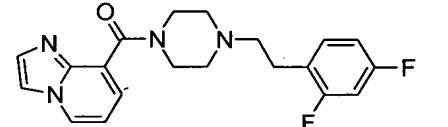
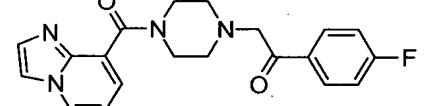
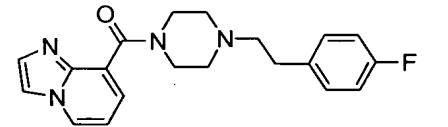
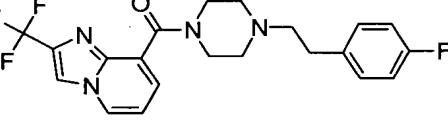
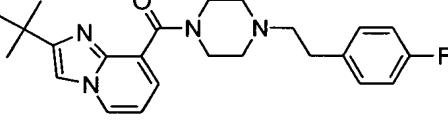
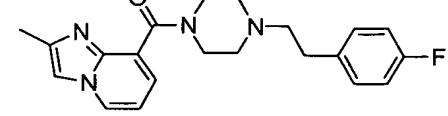
R⁶ and R⁷ are both H;

30 R⁸ and R⁹ are each independently selected from the group consisting of H and F; or
R⁸ and R⁹ together form oxo; and

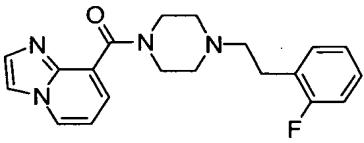
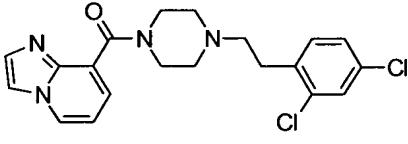
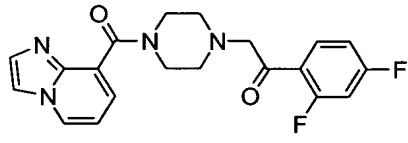
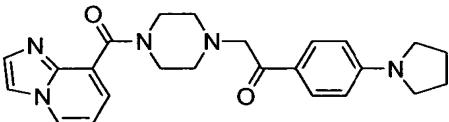
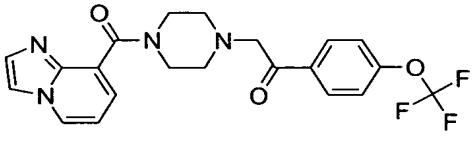
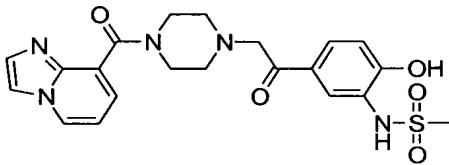
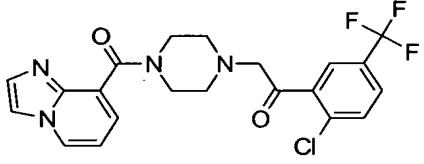
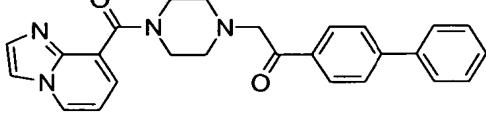
R^{10} , R^{11} , R^{12} , R^{13} and R^{14} are each independently selected from the group consisting of H, methyl, methoxy, dimethylamino, - NHSO_2CH_3 , methylsulfonyl, carboxamide, carboxy, cyano, cyclohexyl, fluoro, chloro, trifluoromethoxy, difluoromethoxy, trifluoromethyl, morpholin-4-yl, pyrrolidin-1-yl, thien-2-yl, hydroxyl, nitro, phenyl and sulfonic acid.

5 Some embodiments of the present invention include every combination of one or more compounds selected from the following group shown in TABLE A.

TABLE A

Cmpd No.	Chemical Structure	Chemical Name
1		(3-bromoimidazo[1,2-a]pyridin-8-yl)(4-(2,4-difluorophenethyl)piperazin-1-yl)methanone
2		8-(4-(2,4-difluorophenethyl)piperazine-1-carbonyl)imidazo[1,2-a]pyridine-3-carbonitrile
3		(4-(2,4-difluorophenethyl)piperazin-1-yl)(imidazo[1,2-a]pyridin-8-yl)methanone
4		1-(4-fluorophenyl)-2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)ethanone
5		(4-(4-fluorophenethyl)piperazin-1-yl)(imidazo[1,2-a]pyridin-8-yl)methanone
6		(4-(4-fluorophenethyl)piperazin-1-yl)(2-(trifluoromethyl)imidazo[1,2-a]pyridin-8-yl)methanone
7		(2-tert-butylimidazo[1,2-a]pyridin-8-yl)(4-(4-fluorophenethyl)piperazin-1-yl)methanone
8		(4-(4-fluorophenethyl)piperazin-1-yl)(2-methylimidazo[1,2-a]pyridin-8-yl)methanone

Cmpd No.	Chemical Structure	Chemical Name
9		(4-(4-fluorophenethyl)piperazin-1-yl)(2-phenylimidazo[1,2-a]pyridin-8-yl)methanone
10		(4-(2-fluoro-2-(4-fluorophenyl)ethyl)piperazin-1-yl)(imidazo[1,2-a]pyridin-8-yl)methanone.
11		(3-chloroimidazo[1,2-a]pyridin-8-yl)(4-(2,4-difluorophenethyl)piperazin-1-yl)methanone
12		imidazo[1,2-a]pyridin-8-yl(4-(4-methoxyphenethyl)piperazin-1-yl)methanone
13		(4-(3,4-dimethoxyphenethyl)piperazin-1-yl)(imidazo[1,2-a]pyridin-8-yl)methanone
14		(4-(3-fluorophenethyl)piperazin-1-yl)(imidazo[1,2-a]pyridin-8-yl)methanone
15		(4-(4-chlorophenethyl)piperazin-1-yl)(imidazo[1,2-a]pyridin-8-yl)methanone
16		(4-(3-chlorophenethyl)piperazin-1-yl)(imidazo[1,2-a]pyridin-8-yl)methanone
17		(4-(2-chlorophenethyl)piperazin-1-yl)(imidazo[1,2-a]pyridin-8-yl)methanone

Cmpd No.	Chemical Structure	Chemical Name
18		(4-(2-fluorophenethyl)piperazin-1-yl)(imidazo[1,2-a]pyridin-8-yl)methanone
19		(4-(2,4-dichlorophenethyl)piperazin-1-yl)(imidazo[1,2-a]pyridin-8-yl)methanone
20		1-(2,4-difluorophenyl)-2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)ethanone
21		2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)-1-(4-(pyrrolidin-1-yl)phenyl)ethanone
22		2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)-1-(4-(trifluoromethoxy)phenyl)ethanone
23		N -(2-hydroxy-5-(2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)acetyl)phenyl)methanesulfonamide
24		1-(2-chloro-5-(trifluoromethyl)phenyl)-2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)ethanone
25		1-(biphenyl-4-yl)-2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)ethanone

Cmpd No.	Chemical Structure	Chemical Name
26		2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)-1-(4-(methylsulfonyl)phenyl)ethanone
27		(4-(2,4-difluorophenethyl)piperazin-1-yl)(5,7-dimethylimidazo[1,2-a]pyridin-8-yl)methanone
28		1-(4-cyclohexylphenyl)-2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)ethanone
29		1-(4-(difluoromethoxy)phenyl)-2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)ethanone
30		2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)-1-phenylpropan-1-one
31		1-(4-chloro-2-fluoro-5-methylphenyl)-2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)ethanone
32		1-(5-chloro-2-methoxy-4-methylphenyl)-2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)ethanone
33		1-(3,5-bis(trifluoromethyl)phenyl)-2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)ethanone

Cmpd No.	Chemical Structure	Chemical Name
34		2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)-1-(4-(trifluoromethyl)phenyl)ethanone
35		2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)-1-(4-(thiophen-2-yl)phenyl)ethanone
36		(4-(2,4-difluorophenethyl)piperazin-1-yl)(7-methoxyimidazo[1,2-a]pyridin-8-yl)methanone
37		2-hydroxy-5-(2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)acetyl)benzamide
38		2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)-1-(4-(trifluoromethyl)phenyl)ethanone
39		4-(2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)acetyl)benzonitrile
40		1-(4-hydroxyphenyl)-2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)ethanone
41		1-(4-(dimethylamino)phenyl)-2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)ethanone

Cmpd No.	Chemical Structure	Chemical Name
42		1-(5-chloro-2-methoxy-4-methyl-3-nitrophenyl)-2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)ethanone
43		2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)-1-(4-morpholinophenyl)ethanone
44		(6-bromoimidazo[1,2-a]pyridin-8-yl)(4-(2,4-difluorophenethyl)piperazin-1-yl)methanone

Additionally, individual compounds and chemical genera of the present invention, for example those compounds found in TABLE A including diastereomers and enantiomers thereof, encompass all pharmaceutically acceptable salts, solvates and particularly hydrates, thereof.

The compounds of the Formula (Ia) of the present invention may be prepared according to relevant published literature procedures that are used by one skilled in the art. Exemplary reagents and procedures for these reactions appear hereinafter in the working Examples. Protection and deprotection may be carried out by procedures generally known in the art (see, for example, Greene, T. W. and Wuts, P. G. M., *Protecting Groups in Organic Synthesis*, 3rd Edition, 1999 [Wiley]; incorporated herein by reference in its entirety).

It is understood that the present invention embraces each diastereomer, each enantiomer and mixtures thereof of each compound and generic formulae disclosed herein just as if they were each individually disclosed with the specific stereochemical designation for each chiral carbon. Separation of the individual isomers (such as, by chiral HPLC, recrystallization of diastereomeric mixtures and the like) or selective synthesis (such as, by enantiomeric selective syntheses and the like) of the individual isomers is accomplished by application of various methods which are well known to practitioners in the art.

INDICATIONS AND METHODS OF TREATMENT

In addition to the foregoing beneficial uses for the modulators of 5-HT_{2A} serotonin receptor activity disclosed herein, the compounds disclosed herein are believed to be useful in the treatment of several additional diseases and disorders and in the amelioration of symptoms thereof. Without limitation, these include the following:

1. Sleep disorders

It is reported in the National Sleep Foundation's 2002 Sleep In America Poll, 58% of the adults surveyed report having experienced one or more symptoms of insomnia at least a few nights a week in the past year. Additionally, 35% of the adults surveyed say they have experienced insomnia-like symptoms every night or almost every night.

The normal sleep cycle and sleep architecture can be disrupted by a variety of organic causes as well as environmental influences. According to the International Classification of Sleep Disorders, there are over 80 recognized sleep disorders. Of these, compounds of the present invention are effective, for example, in any one or more of the following sleep disorders (ICSD-International Classification of Sleep Disorders: Diagnostic and Coding Manual. *Diagnostic Classification Steering Committee*, American Sleep Disorders Association, 1990):

A. Dyssomnias**a. Intrinsic Sleep Disorders:**

Psychophysiological insomnia, sleep state misperception, idiopathic insomnia, obstructive sleep apnea syndrome, central sleep apnea syndrome, central alveolar hypoventilation syndrome, periodic limb movement disorder, restless leg syndrome and intrinsic sleep disorder NOS (not otherwise specified).

b. Extrinsic Sleep Disorders:

Inadequate sleep hygiene, environmental sleep disorder, altitude insomnia, adjustment sleep disorder, insufficient sleep syndrome, limit-setting sleep disorder, sleep onset association disorder, nocturnal eating (drinking) syndrome, hypnotic-dependent sleep disorder, stimulant-dependent sleep disorder, alcohol-dependent sleep disorder, toxin-induced sleep disorder and extrinsic sleep disorder NOS.

c. Circadian Rhythm Sleep Disorders:

Time zone change (jet lag) syndrome, shift work sleep disorder, irregular sleep-wake pattern, delayed sleep phase syndrome, advanced sleep phase syndrome, non-24-hour sleep-wake disorder and circadian rhythm sleep disorder NOS.

B. Parasomnias**a. Arousal Disorders:**

Confusional arousals, sleepwalking and sleep terrors.

b. Sleep-Wake Transition Disorders:

Rhythmic movement disorder, sleep starts, sleep talking and nocturnal leg cramps.

C. Sleep Disorders Associated With Medical/Psychiatric Disorders**a. Associated with Mental Disorders:**

Psychoses, mood disorders, anxiety disorders, panic disorders and alcoholism.

b. Associated with Neurological Disorders:

Cerebral degenerative disorders, dementia, Parkinsonism, fatal familial insomnia, sleep-related epilepsy, electrical status epilepticus of sleep and sleep-related headaches.

c. Associated with Other Medical Disorders:

- Sleeping sickness, nocturnal cardiac ischemia, chronic obstructive pulmonary disease, 5 sleep-related asthma, sleep-related gastroesophageal reflux, peptic ulcer disease, fibrositis syndrome, osteoarthritis, rheumatoid arthritis, fibromyalgia and post-surgical.

The effects of sleep deprivation are more than excessive daytime sleepiness. Chronic insomniacs report elevated levels of stress, anxiety, depression and medical illnesses (National Institutes of Health, National Heart, Lung and Blood Institute, *Insomnia Facts Sheet*, Oct. 1995).

- 10 Preliminary evidence suggests that having a sleep disorder that causes significant loss of sleep may contribute to increased susceptibility to infections due to immunosuppression, cardiovascular complications such as hypertension, cardiac arrhythmias, stroke and myocardial infarction, compromised glucose tolerance, increased obesity and metabolic syndrome. Compounds of the present invention are useful to prevent or alleviate these complications by improving sleep quality.

- 15 The most common class of medications for the majority of sleep disorders are the benzodiazepines, but the adverse effect profile of benzodiazepines includes daytime sedation, diminished motor coordination and cognitive impairments. Furthermore, at the National Institutes of Health Consensus Conference on Sleeping Pills and Insomnia in 1984 guidelines were developed discouraging the use of such sedative-hypnotics beyond 4-6 weeks because of concerns raised over 20 drug misuse, dependency, withdrawal and rebound insomnia. Therefore, it is desirable to have a pharmacological agent for the treatment of insomnia, which is more effective and/or has fewer side effects than those currently used. In addition, benzodiazepines are used to induce sleep, but have little to no effect on the maintenance of sleep, sleep consolidation or slow wave sleep. Therefore, sleep maintenance disorders are not currently well treated.

- 25 Clinical studies with agents of a similar mechanism of action as compounds of the present invention have demonstrated significant improvements on objective and subjective sleep parameters in normal, healthy volunteers as well as patients with sleep disorders and mood disorders [Sharpley A. L., *et al.*, Slow Wave Sleep in Humans: Role of 5-HT_{2A} and 5HT_{2C} Receptors. *Neuropharmacology*, 1994, Vol. 33(3/4):467-71; Winokur A., *et al.*, Acute Effects of 30 Mirtazapine on Sleep Continuity and Sleep Architecture in Depressed Patients: A Pilot Study. *Soc. of Biol. Psych.*, 2000, Vol. 48:75-78; and Landolt H. P., *et al.*, Serotonin-2 Receptors and Human Sleep: Effect of Selective Antagonist on EEG Power Spectra. *Neuropsychopharmacology*, 1999, Vol. 21(3):455-66].

- Some sleep disorders are sometimes found in conjunction with other conditions and 35 accordingly those conditions are treatable by compounds of Formula (Ia). For example, but not limited to, patients suffering from mood disorders typically suffer from a sleep disorder that can be treatable by compounds of Formula (Ia). Having one pharmacological agent which treats two or

more existing or potential conditions, as does the present invention, is more cost effective, leads to better compliance and has fewer side effects than taking two or more agents.

It is an object of the present invention to provide a therapeutic agent for the use in treating sleep disorders. It is another object of the present invention to provide one pharmaceutical agent, which may be useful in treating two or more conditions wherein one of the conditions is a sleep disorder. Compounds of the present invention described herein may be used alone or in combination with a mild sleep inducer (*i.e.* antihistamine).

Sleep Architecture:

Sleep comprises two physiological states: Non rapid eye movement (NREM) and rapid eye movement (REM) sleep. NREM sleep consists of four stages, each of which is characterized by progressively slower brain wave patterns, with the slower patterns indicating deeper sleep. So called delta sleep, stages 3 and 4 of NREM sleep, is the deepest and most refreshing type of sleep. Many patients with sleep disorders are unable to adequately achieve the restorative sleep of stages 3 and 4. In clinical terms, patients' sleep patterns are described as fragmented, meaning patients spend a lot of time alternating between stages 1 and 2 (semi-wakefulness) and being awake and very little time in deep sleep. As used herein, the term "fragmented sleep architecture" means an individual, such as a sleep disorder patient, spends the majority of their sleep time in NREM sleep stages 1 and 2, lighter periods of sleep from which the individual can be easily aroused to a waking state by limited external stimuli. As a result, the individual cycles through frequent bouts of light sleep interrupted by frequent awakenings throughout the sleep period. Many sleep disorders are characterized by fragmented sleep architecture. For example, many elderly patients with sleep complaints have difficulty achieving long bouts of deep, refreshing sleep (NREM stages 3 and 4) and instead spend the majority of their sleep time in NREM sleep stages 1 and 2.

In contrast to fragmented sleep architecture, as used herein the term "sleep consolidation" means a state in which the number of NREM sleep bouts, particularly stages 3 and 4 and the length of those sleep bouts are increased, while the number and length of waking bouts are decreased. In essence, the sleep architecture of the sleep disorder patient is consolidated to a sleeping state with increased periods of sleep and fewer awakenings during the night. More time is spent in slow wave sleep (stages 3 and 4) with fewer oscillations between stages 1 and 2. Compounds of the present invention can be effective in consolidating sleep patterns so that the patient with previously fragmented sleep can now achieve restorative, delta-wave sleep for longer, more consistent periods of time.

As sleep moves from stage 1 into later stages, heart rate and blood pressure drop, metabolic rate and glucose consumption fall and muscles relax. In normal sleep architecture, NREM sleep makes up about 75-80% of total sleep time; stage 1 accounting for 2-5% of total sleep time, stage 2 for about 45-50%, stage 3 approximately 3-8% and stage 4 approximately 10-15%. About 90 minutes after sleep onset, NREM sleep gives way to the first REM sleep episode of the night. REM

makes up approximately 20-25% of total sleep time. In contrast to NREM sleep, REM sleep is characterized by high pulse, respiration and blood pressure, as well as other physiological patterns similar to those seen in the active waking stage. Hence, REM sleep is also known as "paradoxical sleep." Sleep onset occurs during NREM sleep and takes 10-20 minutes in healthy young adults.

5 The four stages of NREM sleep together with a REM phase form one complete sleep cycle that is repeated throughout the duration of sleep, usually four or five times. The cyclical nature of sleep is regular and reliable: a REM period occurs about every 90 minutes during the night. However, the first REM period tends to be the shortest, often lasting less than 10 minutes, whereas the later REM periods may last up to 40 minutes. With aging, the time between retiring and sleep onset increases
10 and the total amount of night-time sleep decreases because of changes in sleep architecture that impair sleep maintenance as well as sleep quality. Both NREM (particularly stages 3 and 4) and REM sleep are reduced. However, stage 1 NREM sleep, which is the lightest sleep, increases with age.

As used herein, the term "delta power" means a measure of the duration of EEG activity in the 0.5
15 to 3.5 Hz range during NREM sleep and is thought to be a measure of deeper, more refreshing sleep. Delta power is hypothesized to be a measure of a theoretical process called Process S and is thought to be inversely related to the amount of sleep an individual experiences during a given sleep period. Sleep is controlled by homeostatic mechanisms; therefore, the less one sleeps the greater the drive to sleep. It is believed that Process S builds throughout the wake period and is
20 discharged most efficiently during delta power sleep. Delta power is a measure of the magnitude of Process S prior to the sleep period. The longer one stays awake, the greater Process S or drive to sleep and thus the greater the delta power during NREM sleep. However, individuals with sleep disorders have difficulty achieving and maintaining delta wave sleep and thus have a large build-up of Process S with limited ability to discharge this buildup during
25 sleep. 5-HT_{2A} agonists tested preclinically and clinically mimic the effect of sleep deprivation on delta power, suggesting that subjects with sleep disorders treated with a 5-HT_{2A} inverse agonist or antagonist will be able to achieve deeper sleep that is more refreshing. These same effects have not been observed with currently marketed pharmacotherapies. In addition,
30 currently marketed pharmacotherapies for sleep have side effects such as hangover effects or addiction that are associated with the GABA receptor. 5-HT_{2A} inverse agonists do not target the GABA receptor and so these side effects are not a concern.

Subjective and objective determinations of sleep disorders:

There are a number of ways to determine whether the onset, duration or quality of sleep (e.g. non-restorative or restorative sleep) is impaired or improved. One method is a subjective
35 determination of the patient, e.g., do they feel drowsy or rested upon waking. Other methods involve the observation of the patient by another during sleep, e.g., how long it takes the patient to

fall asleep, how many times the patient wakes up during the night, how restless is the patient during sleep, etc. Another method is to measure the stages of sleep objectively using polysomnography.

Polysomnography is the monitoring of multiple electrophysiological parameters during sleep and generally includes measurement of EEG activity, electrooculographic activity and electromyographic activity, as well as other measurements. These results, along with observations, can measure not only sleep latency (the amount of time required to fall asleep), but also sleep continuity (overall balance of sleep and wakefulness) and sleep consolidation (percent of sleeping time spent in delta-wave or restorative sleep) which may be an indication of the quality of sleep.

There are five distinct sleep stages, which can be measured by polysomnography: rapid eye movement (REM) sleep and four stages of non-rapid eye movement (NREM) sleep (stages 1, 2, 3 and 4). Stage 1 NREM sleep is a transition from wakefulness to sleep and occupies about 5% of time spent asleep in healthy adults. Stage 2 NREM sleep, which is characterized by specific EEG waveforms (sleep spindles and K complexes), occupies about 45-50% of time spent asleep. Stages 3 and 4 NREM sleep (also known collectively as slow-wave sleep and delta-wave sleep) are the deepest levels of sleep and occupy about 10-20% of sleep time. REM sleep, during which the majority of vivid dreams occur, occupies about 20-25% of total sleep.

These sleep stages have a characteristic temporal organization across the night. NREM stages 3 and 4 tend to occur in the first one-third to one-half of the night and increase in duration in response to sleep deprivation. REM sleep occurs cyclically through the night. Alternating with NREM sleep about every 80-100 minutes. REM sleep periods increase in duration toward the morning. Human sleep also varies characteristically across the life span. After relative stability with large amounts of slow-wave sleep in childhood and early adolescence, sleep continuity and depth deteriorate across the adult age range. This deterioration is reflected by increased wakefulness and stage 1 sleep and decreased stages 3 and 4 sleep.

In addition, the compounds of the invention can be useful for the treatment of the sleep disorders characterized by excessive daytime sleepiness such as narcolepsy. Inverse agonists at the serotonin 5-HT_{2A} receptor improve the quality of sleep at nighttime which can decrease excessive daytime sleepiness.

Accordingly, another aspect of the present invention relates to the therapeutic use of compounds of the present invention for the treatment of sleep disorders. Compounds of the present invention are potent inverse agonists at the serotonin 5-HT_{2A} receptor and can be effective in the treatment of sleep disorders by promoting one or more of the following: reducing the sleep onset latency period (measure of sleep induction), reducing the number of nighttime awakenings and prolonging the amount of time in delta-wave sleep (measure of sleep quality enhancement and sleep consolidation) without effecting REM sleep. In addition, compounds of the present invention can be effective either as a monotherapy or in combination with sleep inducing agents, for example but not limited to, antihistamines.

Pharmacodynamic Effects of the Selective 5-HT_{2A} Inverse Agonist APD125 in Healthy Adults:

APD125, a potent and selective 5-HT_{2A} serotonin receptor inverse agonist is a member of the genus disclosed in the European Patent EP1558582. In Phase 1 trials, APD125 showed 5 vigilance-lowering effects on waking EEG, with maximal effects at 40-80 mg; peak effects were observed at 2-4 h after dosing. In the afternoon nap model of insomnia in normal volunteers, APD125 increased slow wave sleep and associated parameters in a dose-dependent manner, primarily during the early part of sleep. These effects occurred at the expense of REM sleep. Sleep onset latency was not decreased by APD125. In the afternoon nap model, APD125 10 decreased microarousals, the number of sleep stage shifts and number of awakenings after sleep onset.

In conclusion, APD125, a 5-HT_{2A} serotonin receptor inverse agonist, improved 15 parameters of sleep consolidation and maintenance in humans. Thus, compounds of the present invention, also highly selective 5-HT_{2A} serotonin receptor inverse agonists, will offer similar improvements in sleep parameters.

2. Antiplatelet Therapies (Conditions Related to Platelet Aggregation):

Antiplatelet agents (antiplatelets) are prescribed for a variety of conditions. For example, in coronary artery disease they are used to help prevent myocardial infarction or stroke in patients 20 who are at risk of developing obstructive blood clots (*e.g.*, coronary thrombosis).

In a myocardial infarction (heart attack), the heart muscle does not receive enough oxygen-rich blood because of a blockage in the coronary blood vessels. If taken while an attack is in progress or immediately afterward (preferably within 30 minutes), antiplatelets can reduce the damage to the heart.

25 A transient ischemic attack (“TIA” or “mini-stroke”) is a brief interruption of oxygen flow to the brain due to decreased blood flow through arteries, usually due to an obstructing blood clot. Antiplatelet drugs have been found to be effective in preventing TIAs.

Angina is a temporary and often recurring chest pain, pressure or discomfort caused by 30 inadequate oxygen-rich blood flow (ischemia) to some parts of the heart. In patients with angina, antiplatelet therapy can reduce the effects of angina and the risk of myocardial infarction.

Stroke is an event in which the brain does not receive enough oxygen-rich blood, usually due to blockage of a cerebral blood vessel by a blood clot. In high-risk patients, taking antiplatelets regularly has been found to prevent the formation of blood clots that cause first or second strokes.

Angioplasty is a catheter-based technique used to open arteries obstructed by a blood clot. 35 Whether or not stenting is performed immediately after this procedure to keep the artery open, antiplatelets can reduce the risk of forming additional blood clots following the procedure(s).

Coronary bypass surgery is a surgical procedure in which an artery or vein is taken from elsewhere in the body and grafted to a blocked coronary artery, rerouting blood around the blockage and through the newly attached vessel. After the procedure, antiplatelets can reduce the risk of secondary blood clots.

5 Atrial fibrillation is the most common type of sustained irregular heart rhythm (arrhythmia). Atrial fibrillation affects about two million Americans every year. In atrial fibrillation, the atria (the heart's upper chambers) rapidly fire electrical signals that cause them to quiver rather than contract normally. The result is an abnormally fast and highly irregular heartbeat. When given after an episode of atrial fibrillation, antiplatelets can reduce the risk of blood clots
10 forming in the heart and traveling to the brain (embolism).

5-HT_{2A} serotonin receptors are expressed on smooth muscle of blood vessels and 5-HT secreted by activated platelets causes vasoconstriction as well as activation of additional platelets during clotting. There is evidence that a 5-HT_{2A} inverse agonist will inhibit platelet aggregation and thus be a potential treatment as an antiplatelet therapy (see Satimura, K., *et al.*, *Clin. Cardiol.*

15 2002 Jan. 25 (1):28-32; and Wilson, H. C. *et al.*, *Thromb. Haemost.* 1991 Sep 2;66(3):355-60).

5-HT_{2A} inverse agonists can be used to treat, for example, claudication or peripheral artery disease as well as cardiovascular complications (see *Br. Med. J.* 298: 424-430, 1989), arterial thrombosis (see, Pawlak, D. *et al.*, *Thrombosis Research* 90: 259-270, 1998), atherosclerosis (see, Hayashi, T. *et al.*, *Atherosclerosis* 168: 23-31, 2003), vasoconstriction caused by serotonin (see, Fujiwara, T. and Chiba, S. *Journal of Cardiovascular Pharmacology* 26: 503-510, 1995), restenosis of arteries following angioplasty or stent placement (see, Fujita, M. *et al.*, *Am. Heart J.* 145:e16, 2003). It can also be used alone or in combination with thrombolytic therapy, for example, tissue plasminogen activator (tPA) (see, Yamashita, T. *et al.*, *Haemostasis* 30:321-332, 2000), to provide cardioprotection following MI or postischemic myocardial dysfunction (see, Muto, T. *et al.*, *Mol. Cell. Biochem.* 272: 119-132, 2005) or protection from ischemic injury during percutaneous coronary intervention (see, Horibe, E. *Circulation Research* 68: 68-72, 2004) and the like, including complications resulting therefrom.

5-HT_{2A} inverse antagonists can increase circulating adiponectin in patients, suggesting that they would also be useful in protecting patients against indications that are linked to adiponectin, for example, myocardial ischemia reperfusion injury and atherosclerosis (see Nomura *et al.*, *Blood Coagulation and Fibrinolysis* 2005, 16, 423-428).

The 5-HT_{2A} inverse agonists disclosed herein provide beneficial improvement in microcirculation to patients in need of antiplatelet therapy by antagonizing the vasoconstrictive products of the aggregating platelets in, for example and not limited to the indications described above. Accordingly, in some embodiments, the present invention provides methods for reducing platelet aggregation in a patient in need thereof comprising administering to the patient a

composition comprising a 5-HT_{2A} inverse agonist disclosed herein. In further embodiments, the present invention provides methods for treating coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, or a symptom of any of the foregoing in a patient in need of the treatment, comprising administering to the patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein.

In further embodiments, the present invention provides methods for reducing risk of blood clot formation in an angioplasty or coronary bypass surgery patient, or a patient suffering from atrial fibrillation, comprising administering to the patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein at a time where such risk exists.

10

3. **Asthma**

5-HT has been linked to the pathophysiology of acute asthma (see Cazzola, M. and Matera, M. G., *Trends Pharmacol. Sci.* 21: 201-202, 2000; and De Bie, J. J. *et al.*, *British J. Pharm.*, 1998, 124, 857-864). The compounds of the present invention disclosed herein are useful in the treatment of asthma and the treatment of the symptoms thereof. Accordingly, in some embodiments, the present invention provides methods for treating asthma in a patient in need of the treatment, comprising administering to the patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein. In further embodiments, methods are provided for treating a symptom of asthma in a patient in need of the treatment, comprising administering to the patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein.

4. **Agitation**

Agitation is a well-recognized behavioral syndrome with a range of symptoms, including hostility, extreme excitement, poor impulse control, tension and uncooperativeness (see Cohen-Mansfield J. and Billig, N., (1986), Agitated Behaviors in the Elderly. I. A Conceptual Review. *J. Am. Geriatr. Soc.* 34(10): 711-721).

Agitation is a common occurrence in the elderly and is often associated with dementia such as those caused by Alzheimer's disease, Lewy Body, Parkinson's and Huntington's, which are degenerative diseases of the nervous system. Diseases that affect blood vessels, such as stroke, or multi-infarct dementia, which is caused by multiple strokes in the brain can also induce agitation. Alzheimer's disease accounts for approximately 50 to 70% of all dementias (see Koss E., *et al.*, (1997), Assessing patterns of agitation in Alzheimer's disease patients with the Cohen-Mansfield Agitation Inventory. The Alzheimer's Disease Cooperative Study. *Alzheimer Dis. Assoc. Disord.* 11(suppl 2):S45-S50).

An estimated 5% of people aged 65 and older and up to 20% of those aged 80 and older are affected by dementia; of these sufferers, nearly half exhibit behavioral disturbances, such as agitation, wandering and violent outbursts.

Agitated behaviors can also be manifested in cognitively intact elderly people and by those with psychiatric disorders other than dementia.

Agitation is often treated with antipsychotic medications such as haloperidol in nursing home and other assisted care settings. There is emerging evidence that agents acting at the 5-HT_{2A} serotonin receptors in the brain have the effects of reducing agitation in patients, including Alzheimer's dementia (See Katz, I. R., *et al.*, *J. Clin. Psychiatry* 1999 Feb., 60(2):107-115; and Street, J. S., *et al.*, *Arch. Gen. Psychiatry* 2000 Oct., 57(10):968-976).

The compounds of the invention disclosed herein are useful for treating agitation and symptoms thereof. Thus, in some embodiments, the present invention provides methods for treating agitation in a patient in need of such treatment comprising administering to the patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein. In some embodiments, the agitation is due to a psychiatric disorder other than dementia. In some embodiments, the present invention provides methods for treatment of agitation or a symptom thereof in a patient suffering from dementia comprising administering to the patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein. In some embodiments of such methods, the dementia is due to a degenerative disease of the nervous system, for example and without limitation, Alzheimer's disease, Lewy Body, Parkinson's disease and Huntington's disease, or dementia due to diseases that affect blood vessels, including, without limitation, stroke and multi-infarct dementia. In some embodiments, methods are provided for treating agitation or a symptom thereof in a patient in need of such treatment, where the patient is a cognitively intact elderly patient, comprising administering to the patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein.

5. Add-On therapy to Haloperidol in the treatment of schizophrenia and other disorders:

Schizophrenia is a psychopathic disorder of unknown origin, which usually appears for the first time in early adulthood and is marked by a number of characteristics, psychotic symptoms, progression, phasic development and deterioration in social behavior and professional capability in the region below the highest level ever attained. Characteristic psychotic symptoms are disorders of thought content (multiple, fragmentary, incoherent, implausible or simply delusional contents or ideas of persecution) and of mentality (loss of association, flight of imagination, incoherence up to incomprehensibility), as well as disorders of perceptibility (hallucinations), of emotions (superficial or inadequate emotions), of self-perception, of intentions and impulses, of interhuman relationships and finally psychomotoric disorders (such as catatonia). Other symptoms are also associated with this disorder: see, *American Statistical and Diagnostic Handbook*.

Haloperidol (Haldol) is a potent dopamine D₂ receptor antagonist. It is widely prescribed for acute schizophrenic symptoms and is very effective for the positive symptoms of schizophrenia. However, Haldol is not effective for the negative symptoms of schizophrenia and may actually

induce negative symptoms as well as cognitive dysfunction. In accordance with some methods of the invention, administering a 5-HT_{2A} inverse agonist concomitantly with Haldol will provide benefits including the ability to use a lower dose of Haldol without losing its effects on positive symptoms, while reducing or eliminating its inductive effects on negative symptoms and
5 prolonging relapse to the patient's next schizophrenic event.

Haloperidol is used for treatment of a variety of behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorders, psychosis (organic and NOS), psychotic disorder, psychosis, schizophrenia (acute, chronic and NOS). Further uses include in the treatment of infantile autism, Huntington's chorea and nausea and vomiting from
10 chemotherapy and chemotherapeutic antibodies. Administration of 5-HT_{2A} inverse agonists disclosed herein with haloperidol also will provide benefits in these indications.

In some embodiments, the present invention provides methods for treating a behavioral disorder, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorders, psychosis (organic and NOS), psychotic disorder, psychosis, schizophrenia (acute,
15 chronic and NOS) comprising administering to the patient a dopamine D₂ receptor antagonist and a 5-HT_{2A} inverse agonist disclosed herein.

In some embodiments, the present invention provides methods for treating a behavioral disorder, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorders, psychosis (organic and NOS), psychotic disorder, psychosis, schizophrenia (acute,
20 chronic and NOS) comprising administering to the patient haloperidol and a 5-HT_{2A} inverse agonist disclosed herein.

In some embodiments, the present invention provides methods for treating infantile autism, Huntington's chorea, or nausea and vomiting from chemotherapy or chemotherapeutic antibodies comprising administering to the patient a dopamine D₂ receptor antagonist and a 5-HT_{2A} inverse
25 agonist disclosed herein.

In some embodiments, the present invention provides methods for treating infantile autism, Huntington's chorea, or nausea and vomiting from chemotherapy or chemotherapeutic antibodies comprising administering to the patient haloperidol and a 5-HT_{2A} inverse agonist disclosed herein.

In further embodiments, the present invention provides methods for treating schizophrenia
30 in a patient in need of the treatment comprising administering to the patient a dopamine D₂ receptor antagonist and a 5-HT_{2A} inverse agonist disclosed herein. Preferably, the dopamine D₂ receptor antagonist is haloperidol.

The administration of the dopamine D₂ receptor antagonist can be concomitant with administration of the 5-HT_{2A} inverse agonist, or they can be administered at different times. Those
35 of skill in the art will easily be able to determine appropriate dosing regimes for the most efficacious reduction or elimination of deleterious haloperidol effects. In some embodiments,

haloperidol and the 5-HT_{2A} inverse agonist are administered in a single dosage form and in other embodiments, they are administered in separate dosage forms.

The present invention further provides methods of alleviating negative symptoms of schizophrenia induced by the administration of haloperidol to a patient suffering from schizophrenia, comprising administering to the patient a 5-HT_{2A} inverse agonist as disclosed herein.

6. Diabetic-Related Pathologies:

Although hyperglycemia is the major cause for the pathogenesis of diabetic complications such as diabetic peripheral neuropathy (DPN), diabetic nephropathy (DN) and diabetic retinopathy (DR), some clinical work has implicated that increased plasma serotonin concentration in diabetic patients plays a role in disease progression (Pietraszek, M. H., *et al.*, *Thrombosis Res.* 1992, 66(6), 765-74; and Andrzejewska-Buczko J., *et al.*, *Klin. Oczna.* 1996; 98(2), 101-4). Serotonin is believed to play a role in vasospasm and increased platelet aggregability. Improving microvascular blood flow is beneficial to diabetic complications.

A recent study by Cameron and Cotter in *Naunyn Schmiedebergs Arch. Pharmacol.* 2003 Jun; 367(6):607-14, used a 5-HT_{2A} antagonist experimental drug AT-1015 and other non-specific 5-HT_{2A} antagonists including ritanserin and sarpogrelate. These studies found that all three drugs were able to produce a marked correction (82.6-99.7%) of a 19.8% sciatic motor conduction deficit in diabetic rats. Similarly, 44.7% and 14.9% reductions in sciatic endoneurial blood flow and saphenous sensory conduction velocity were completely reversed.

In a separate patient study, sarpogrelate was evaluated for the prevention of the development or progression of diabetic nephropathy (Takahashi, T., *et al.*, *Diabetes. Res. Clin. Pract.* 2002 Nov; 58(2):123-9). In the trial of 24 months of treatment, sarpogrelate significantly reduced urinary albumin excretion level.

25

7. Glaucoma

Topical ocular administration of 5-HT₂ receptor antagonists result in a decrease in intraocular pressure (IOP) in monkeys (Chang *et al.*, *J. Ocul. Pharmacol.* 1:137-147 (1985)) and humans (Mastropasqua *et al.*, *Acta. Ophthalmol. Scand. Suppl.* 224:24-25 (1997)) indicating utility for similar compounds such as 5-HT_{2A} inverse agonists in the treatment of ocular hypertension associated with glaucoma. The 5-HT₂ receptor antagonist ketanserin (Mastropasqua *supra*) and sarpogrelate (Takenaka *et al.*, *Investig. Ophthalmol. Vis. Sci.* 36:S734 (1995)) have been shown to significantly lower IOP in glaucoma patients.

35 8. Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a lethal demyelinating disease caused by an opportunistic viral infection of oligodendrocytes in immunocompromised patients.

The causative agent is JC virus, a ubiquitous papovavirus that infects the majority of the population before adulthood and establishes a latent infection in the kidney. In immunocompromised hosts, the virus can reactivate and productively infect oligodendrocytes. This previously rare condition, until 1984 reported primarily in persons with underlying lymphoproliferative disorders, is now more common because it occurs in 4% of patients with AIDS. Patients usually present with relentlessly progressive focal neurologic defects, such as hemiparesis or visual field deficits, or with alterations in mental status. On brain MRI, one or more white matter lesions are present; they are hyperintense on T2-weighted images and hypointense on T1-weighted images. There is no mass effect and contrast enhancement is rare. Diagnosis can be confirmed by brain biopsy, with demonstration of virus by *in situ* hybridization or immunocytochemistry. Polymerase chain reaction amplification of JC virus sequences from the CSF can confirm diagnosis without the need for biopsy [Antinori *et al.*, *Neurology* (1997) 48:687-694; Berger and Major, *Seminars in Neurology* (1999) 19:193-200; and Portegies, *et al.*, *Eur. J. Neurol.* (2004) 11:297-304]. Currently, there is no effective therapy. Survival after diagnosis is about 3 to 5 months in AIDS patients.

JC virus enters cells by receptor-mediated clathrin-dependent endocytosis. Binding of JC virus to human glial cells (*e.g.*, oligodendrocytes) induces an intracellular signal that is critical for entry and infection by a ligand-inducible clathrin-dependent mechanism [Querbes *et al.*, *J. Virology* (2004) 78:250-256]. Recently, 5-HT_{2A} was shown to be the receptor on human glial cells mediating infectious entry of JC virus by clathrin-dependent endocytosis [Elphick *et al.*, *Science* (2004) 306:1380-1383]. 5-HT_{2A} antagonists, including ketanserin and ritanserin, inhibited JC virus infection of human glial cells. Ketanserin and ritanserin have inverse agonist activity at 5-HT_{2A}.

5-HT_{2A} antagonists including inverse agonists have been contemplated to be useful in the treatment of PML [Elphick *et al.*, *Science* (2004) 306:1380-1383]. Prophylactic treatment of HIV-infected patients with 5-HT_{2A} antagonists is envisioned to prevent the spread of JC virus to the central nervous system and the development of PML. Aggressive therapeutic treatment of patients with PML is envisioned to reduce viral spread within the central nervous system and prevent additional episodes of demyelination.

One aspect of the present invention encompasses methods for the treatment of progressive multifocal leukoencephalopathy in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound according to any of the embodiments described herein or a pharmaceutical composition.

In some embodiments, the individual in need thereof has a lymphoproliferative disorder. In some embodiments, the lymphoproliferative disorder is leukemia or lymphoma. In some embodiments, the leukemia or lymphoma is chronic lymphocytic leukemia, Hodgkin's disease, or the like.

In some embodiments, the individual in need thereof has a myeloproliferative disorder.

In some embodiments, the individual in need thereof has carcinomatosis.

In some embodiments, the individual in need thereof has a granulomatous or inflammatory disease. In some embodiments, the granulomatous or inflammatory disease is 5 tuberculosis or sarcoidosis.

In some embodiments, the individual in need thereof is immunocompromised. In some embodiments, the immunocompromised individual has impaired cellular immunity. In some embodiments, the impaired cellular immunity comprises impaired T-cell immunity.

In some embodiments, the individual in need thereof is infected with HIV. In some 10 embodiments, the HIV-infected individual has a CD4+ cell count of $\leq 200/\text{mm}^3$. In some embodiments, the HIV-infected individual has AIDS. In some embodiments, the HIV-infected individual has AIDS-related complex (ARC). In certain embodiments, ARC is defined as the presence of two successive CD4+ cell counts below $200/\text{mm}^3$ and at least two of the following signs or symptoms: oral hairy leukoplakia, recurrent oral candidiasis, weight loss of at least 15 lb or 10% of body weight within last six months, multidermatomal herpes zoster, temperature above 38.5°C for more than 14 consecutive days or more than 15 days in a 30-day period, or diarrhea with more than three liquid stools per day for at least 30 days [see, e.g., Yamada *et al.*, *Clin. Diagn. Virol.* (1993) 1:245-256].

In some embodiments, the individual in need thereof is undergoing immunosuppressive 20 therapy. In some embodiments, the immunosuppressive therapy comprises administering an immunosuppressive agent [see, e.g., Mueller, *Ann. Thorac. Surg.* (2004) 77:354-362; and Krieger and Emre, *Pediatr. Transplantation* (2004) 8:594-599]. In some embodiments, the immunosuppressive therapy comprises administering an immunosuppressive agent selected from the group consisting of: corticosteroids (for example, prednisone and the like), calcineurin 25 inhibitors (for example, cyclosporine, tacrolimus and the like), antiproliferative agents (for example, azathioprine, mycophenolate mofetil, sirolimus, everolimus and the like), T-cell depleting agents (for example, OKT[®]3 monoclonal antibody (mAb), anti-CD3 immunotoxin FN18-CRM9, Campath-1H (anti-CD52) mAb, anti-CD4 mAb, anti-T cell receptor mAb and the like), anti-IL-2 receptor (CD25) mAb (for example, basiliximab, daclizumab and the like), 30 inhibitors of co-stimulation (for example, CTLA4-Ig, anti-CD154 (CD40 ligand) mAb and the like), deoxyspergualin and analogs thereof (for example, 15-DSG, LF-08-0299, LF14-0195 and the like), leflunomide and analogs thereof (for example, leflunomide, FK778, FK779 and the like), FTY720, anti-alpha-4-integrin monoclonal antibody and anti-CD45 RB monoclonal antibody. In some embodiments, the immunosuppressive agent and said compound or 35 pharmaceutical composition are administered in separate dosage forms. In some embodiments, the immunosuppressive agent and said compound or pharmaceutical composition are administered in a single dosage form.

In some embodiments, the individual in need thereof is undergoing immunosuppressive therapy after organ transplantation. In some embodiments, the organ is liver, kidney, lung, heart, or the like [see, e.g., Singh *et al.*, *Transplantation* (2000) 69:467-472].

5 In some embodiments, the individual in need thereof is undergoing treatment for a rheumatic disease. In some embodiments, the rheumatic disease is systemic lupus erythematosus or the like.

In some embodiments, the compound or the pharmaceutical composition inhibits JC virus infection of human glial cells

10 **9. Hypertension**

Serotonin has been observed to play an important role in the regulation of vascular tone, vasoconstriction and pulmonary hypertension (Deuchar, G. *et al.*, *Pulm. Pharmacol. Ther.* 18(1):23-31. 2005; and Marcos, E. *et al.*, *Circ. Res.* 94(9):1263-70 2004). Ketanserin, a 5-HT_{2A} inverse agonist, have been demonstrated to protect against circulatory shocks, intracranial hypertension and cerebral ischemia during heatstroke (Chang, C. *et al.*, *Shock* 24(4): 336-340 2005); and to stabilize blood pressure in spontaneously hypertensive rats (Miao, C. *Clin. Exp. Pharmacol. Physiol.* 30(3): 189-193). Mainserin, a 5-HT_{2A} inverse agonist, has been shown to prevent DOCA-salt induced hypertension in rats (Silva, A. *Eur. J. Pharmacol.* 518(2-3): 152-7 2005).

20

10. Pain

5-HT_{2A} inverse agonists are also effective for the treatment of pain. Sarpogrelate has been observed to provide a significant analgesic effect both on thermal induced pain in rats after intraperitoneal administration and on inflammatory pain in rats after either intrathecal or 25 intraperitoneal administration (Nishiyama, T. *Eur. J. Pharmacol.* 516:18-22 2005). This same 5-HT_{2A} inverse agonist in humans has been shown to be an effective treatment for lower back pain, leg pain and numbness associated with sciatica brought on by lumbar disc herniation (Kanayama, M. *et al.*, *J. Neurosurg.: Spine* 2:441-446 2005).

30 **PHARMACEUTICAL COMPOSITIONS**

A further aspect of the present invention pertains to pharmaceutical compositions comprising one or more compounds as described herein and one or more pharmaceutically acceptable carriers. Some embodiments pertain to pharmaceutical compositions comprising a compound of the present invention and a pharmaceutically acceptable carrier.

35

Some embodiments of the present invention include a method of producing a pharmaceutical composition comprising admixing at least one compound according to any of the compound embodiments disclosed herein and a pharmaceutically acceptable carrier.

Formulations may be prepared by any suitable method, typically by uniformly mixing the active compound(s) with liquids or finely divided solid carriers, or both, in the required proportions and then, if necessary, forming the resulting mixture into a desired shape.

Conventional excipients, such as binding agents, fillers, acceptable wetting agents, 5 tabletting lubricants and disintegrants may be used in tablets and capsules for oral administration. Liquid preparations for oral administration may be in the form of solutions, emulsions, aqueous or oily suspensions and syrups. Alternatively, the oral preparations may be in the form of dry powder that can be reconstituted with water or another suitable liquid vehicle before use. Additional additives such as suspending or emulsifying agents, non-aqueous 10 vehicles (including edible oils), preservatives and flavorings and colorants may be added to the liquid preparations. Parenteral dosage forms may be prepared by dissolving the compound of the invention in a suitable liquid vehicle and filter sterilizing the solution before filling and sealing an appropriate vial or ampule. These are just a few examples of the many appropriate methods well known in the art for preparing dosage forms.

15 A compound of the present invention can be formulated into pharmaceutical compositions using techniques well known to those in the art. Suitable pharmaceutically-acceptable carriers, outside those mentioned herein, are known in the art; for example, see Remington, *The Science and Practice of Pharmacy*, 20th Edition, 2000, Lippincott Williams & Wilkins, (Editors: Gennaro *et al.*)

20 While it is possible that, for use in the prophylaxis or treatment, a compound of the invention may, in an alternative use, be administered as a raw or pure chemical, it is preferable however to present the compound or active ingredient as a pharmaceutical formulation or composition further comprising a pharmaceutically acceptable carrier.

25 The invention thus further provides pharmaceutical formulations comprising a compound of the invention or a pharmaceutically acceptable salt, solvate, hydrate or derivative thereof together with one or more pharmaceutically acceptable carriers thereof and/or prophylactic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not overly deleterious to the recipient thereof.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical 30 (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation, insufflation or by a transdermal patch. Transdermal patches dispense a drug at a controlled rate by presenting the drug for absorption in an efficient manner with a minimum of degradation of the drug. Typically, transdermal patches comprise an impermeable backing layer, a single 35 pressure sensitive adhesive and a removable protective layer with a release liner. One of ordinary skill in the art will understand and appreciate the techniques appropriate for manufacturing a desired efficacious transdermal patch based upon the needs of the artisan.

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical formulations and unit dosages thereof and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, gels or capsules filled with the same, all for 5 oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended 10 daily dosage range to be employed.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are capsules, tablets, powders, granules or a suspension, with 15 conventional additives such as lactose, mannitol, corn starch or potato starch; with binders such as crystalline cellulose, cellulose derivatives, acacia, corn starch or gelatins; with disintegrators such as corn starch, potato starch or sodium carboxymethyl-cellulose; and with lubricants such as talc or magnesium stearate. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable 20 pharmaceutically acceptable carrier.

Compounds of the present invention or a solvate or physiologically functional derivative thereof can be used as active ingredients in pharmaceutical compositions, specifically as 5-HT_{2A} serotonin receptor modulators. By the term "active ingredient" is defined in the context of a "pharmaceutical composition" and is intended to mean a component of a pharmaceutical 25 composition that provides the primary pharmacological effect, as opposed to an "inactive ingredient" which would generally be recognized as providing no pharmaceutical benefit.

The dose when using the compounds of the present invention can vary within wide limits and as is customary and is known to the physician, it is to be tailored to the individual conditions in each individual case. It depends, for example, on the nature and severity of the 30 illness to be treated, on the condition of the patient, on the compound employed or on whether an acute or chronic disease state is treated or prophylaxis is conducted or on whether further active compounds are administered in addition to the compounds of the present invention. Representative doses of the present invention include, but not limited to, about 0.001 mg to about 5000 mg, about 0.001 mg to about 2500 mg, about 0.001 mg to about 1000 mg, 0.001 mg 35 to about 500 mg, 0.001 mg to about 250 mg, about 0.001 mg to 100 mg, about 0.001 mg to about 50 mg and about 0.001 mg to about 25 mg. Multiple doses may be administered during the day, especially when relatively large amounts are deemed to be needed, for example 2, 3 or

4 doses. Depending on the individual and as deemed appropriate from the patient's physician or caregiver it may be necessary to deviate upward or downward from the doses described herein.

The amount of active ingredient, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will ultimately be at the discretion of the attendant physician or clinician. In general, one skilled in the art understands how to extrapolate *in vivo* data obtained in a model system, typically an animal model, to another, such as a human. In some circumstances, these extrapolations may merely be based on the weight of the animal model in comparison to another, such as a mammal, preferably a human, however, more often, these extrapolations are not simply based on weights, but rather incorporate a variety of factors. Representative factors include the type, age, weight, sex, diet and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized, on whether an acute or chronic disease state is being treated or prophylaxis is conducted or on whether further active compounds are administered in addition to the compounds of the present invention and as part of a drug combination. The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety factors as cited above. Thus, the actual dosage regimen employed may vary widely and therefore may deviate from a preferred dosage regimen and one skilled in the art will recognize that dosage and dosage regimen outside these typical ranges can be tested and, where appropriate, may be used in the methods of this invention.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day.

The sub-dose itself may be further divided, *e.g.*, into a number of discrete loosely spaced administrations. The daily dose can be divided, especially when relatively large amounts are administered as deemed appropriate, into several, for example 2, 3 or 4 part administrations. If appropriate, depending on individual behavior, it may be necessary to deviate upward or downward from the daily dose indicated.

The compounds of the present invention can be administrated in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either a compound of the invention or a pharmaceutically acceptable salt, solvate or hydrate of a compound of the invention.

For preparing pharmaceutical compositions from the compounds of the present invention, the selection of a suitable pharmaceutically acceptable carrier can be either solid, liquid or a mixture of both. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories and dispersible granules. A solid carrier can be one or more substances

which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

5 In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted to the desire shape and size. The powders and tablets may contain varying percentage amounts of the active compound. A representative amount in a powder or tablet may contain from 0.5 to about 90 percent of the active compound; however, an artisan would know when amounts outside of this range are
10 necessary. Suitable carriers for powders and tablets are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is
15 surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as an admixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously
20 therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool and thereby to solidify.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

25 Liquid form preparations include solutions, suspensions and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution. Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile
30 injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed
35 including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds according to the present invention may thus be formulated for parenteral administration (*e.g.* by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The pharmaceutical compositions may 5 take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles and may contain formulation agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, *e.g.* sterile, pyrogen-free water, before use.

10 Aqueous formulations suitable for oral use can be prepared by dissolving or suspending the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents, as desired.

15 Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well-known suspending agents.

20 Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents and the like.

For topical administration to the epidermis the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch.

25 Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents.

30 Formulations suitable for topical administration in the mouth include lozenges comprising active agent in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multi-dose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case 35 of a spray, this may be achieved for example by means of a metering atomizing spray pump.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurized pack with a suitable

propellant. If the compounds of the present invention or pharmaceutical compositions comprising them are administered as aerosols, for example as nasal aerosols or by inhalation, this can be carried out, for example, using a spray, a nebulizer, a pump nebulizer, an inhalation apparatus, a metered inhaler or a dry powder inhaler. Pharmaceutical forms for administration 5 of the compounds of the present invention as an aerosol can be prepared by processes well known to the person skilled in the art. For their preparation, for example, solutions or dispersions of the compounds of the present invention in water, water/alcohol mixtures or suitable saline solutions can be employed using customary additives, for example benzyl alcohol or other suitable preservatives, absorption enhancers for increasing the bioavailability, 10 solubilizers, dispersants and others and, if appropriate, customary propellants, for example include carbon dioxide, CFCs, such as, dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane; and the like. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

In formulations intended for administration to the respiratory tract, including intranasal 15 formulations, the compound will generally have a small particle size for example of the order of 10 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization. When desired, formulations adapted to give sustained release of the active ingredient may be employed.

Alternatively the active ingredients may be provided in the form of a dry powder, for 20 example, a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active 25 component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can 30 be the appropriate number of any of these in packaged form.

Tablets or capsules for oral administration and liquids for intravenous administration are preferred compositions.

The compounds according to the invention may optionally exist as pharmaceutically acceptable salts including pharmaceutically acceptable acid addition salts prepared from 35 pharmaceutically acceptable non-toxic acids including inorganic and organic acids. Representative acids include, but are not limited to, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, dichloroacetic, formic, fumaric, gluconic, glutamic,

hippuric, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, oxalic, pamoic, pantothenic, phosphoric, succinic, sulfiric, tartaric, oxalic, p-toluenesulfonic and the like, such as those pharmaceutically acceptable salts listed in *Journal of Pharmaceutical Sciences*, 66:1-19 (1977), incorporated herein by reference in its entirety.

The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent. The compounds of this invention may form solvates with standard low molecular weight solvents using methods known to the skilled artisan.

Compounds of the present invention can be converted to “pro-drugs.” The term “pro-drugs” refers to compounds that have been modified with specific chemical groups known in the art and when administered into an individual these groups undergo biotransformation to give the parent compound. Pro-drugs can thus be viewed as compounds of the invention containing one or more specialized non-toxic protective groups used in a transient manner to alter or to eliminate a property of the compound. In one general aspect, the “pro-drug” approach is utilized to facilitate oral absorption. A thorough discussion is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* Vol. 14 of the A.C.S. Symposium Series; and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are hereby incorporated by reference in their entirety.

Some embodiments of the present invention include a method of producing a pharmaceutical composition for “combination-therapy” comprising admixing at least one compound according to any of the compound embodiments disclosed herein, together with at least one known pharmaceutical agent as described herein and a pharmaceutically acceptable carrier.

It is noted that when the 5-HT_{2A} serotonin receptor modulators are utilized as active ingredients in a pharmaceutical composition, these are not intended for use only in humans, but in other non-human mammals as well. Indeed, recent advances in the area of animal health-care mandate that consideration be given for the use of active agents, such as 5-HT_{2A} serotonin receptor modulators, for the treatment of a 5-HT_{2A}-associated disease or disorder in companionship animals (*e.g.*, cats, dogs, *etc.*) and in livestock animals (*e.g.*, cows, chickens, fish, *etc.*) Those of ordinary skill in the art are readily credited with understanding the utility of such compounds in such settings.

OTHER UTILITIES

Another object of the present invention relates to radio-labeled compounds of the present invention that would be useful not only in radio-imaging but also in assays, both *in vitro* and *in vivo*, for localizing and quantitating the 5-HT_{2A} serotonin receptor in tissue samples, including human and for identifying 5-HT_{2A} serotonin receptor ligands by inhibition binding of a radio-labeled compound. It is a further object of this invention to develop novel 5-HT_{2A}-receptor assays of which comprise such radio-labeled compounds.

The present invention embraces isotopically-labeled compounds of the present invention. Isotopically or radio-labeled compounds are those which are identical to compounds disclosed herein, but for the fact that one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number most commonly found in nature. Suitable radionuclides that may be incorporated in compounds of the present invention include but are not limited to ²H (also written as D for deuterium), ³H (also written as T for tritium), ¹¹C, ¹³C, ¹⁴C, ¹³N, ¹⁵N, ¹⁵O, ¹⁷O, ¹⁸O, ¹⁸F, ³⁵S, ³⁶Cl, ⁷⁵Br, ⁷⁶Br, ⁷⁷Br, ⁸²Br, ¹²³I, ¹²⁴I, ¹²⁵I and ¹³¹I. The radionuclide that is incorporated in the instant radio-labeled compounds will depend on the specific application of that radio-labeled compound. For example, for *in vitro* 5-HT_{2A} serotonin receptor labeling and competition assays, compounds that incorporate ³H, ¹⁴C, ⁸²Br, ¹²⁵I, ¹³¹I or ³⁵S will generally be most useful. For radio-imaging applications ¹¹C, ¹⁸F, ¹²⁵I, ¹²³I, ¹²⁴I, ¹³¹I, ⁷⁵Br, ⁷⁶Br or ⁷⁷Br will generally be most useful.

It is understood that a "radio-labeled" or "labeled compound" is a compound of Formula (Ia), (Ic) or (Ie) that has incorporated at least one radionuclide; in some embodiments the radionuclide is selected from the group consisting of ³H, ¹⁴C, ¹²⁵I, ³⁵S and ⁸²Br.

Certain isotopically-labeled compounds of the present invention are useful in compound and/or substrate tissue distribution assays. In some embodiments the radionuclide ³H and/or ¹⁴C isotopes are useful in these studies. Further, substitution with heavier isotopes such as deuterium (*i.e.*, ²H) may afford certain therapeutic advantages resulting from greater metabolic stability (*e.g.*, increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labeled compounds of the present invention can generally be prepared by following procedures analogous to those disclosed in the Drawings and Examples *infra*, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent. Other synthetic methods that are useful are discussed *infra*. Moreover, it should be understood that all of the atoms represented in the compounds of the invention can be either the most commonly occurring isotope of such atoms or the scarcer radio-isotope or nonradioactive isotope.

Synthetic methods for incorporating radio-isotopes into organic compounds are applicable to compounds of the invention and are well known in the art. These synthetic methods, for example, incorporating activity levels of tritium into target molecules, are as follows:

A. Catalytic Reduction with Tritium Gas: This procedure normally yields high specific activity products and requires halogenated or unsaturated precursors.

B. Reduction with Sodium Borohydride [³H]: This procedure is rather inexpensive and requires precursors containing reducible functional groups such as aldehydes, ketones, lactones, esters and the like.

C. Reduction with Lithium Aluminum Hydride [³H]: This procedure offers products at almost theoretical specific activities. It also requires precursors containing reducible functional groups such as aldehydes, ketones, lactones, esters and the like.

D. Tritium Gas Exposure Labeling: This procedure involves exposing precursors containing exchangeable protons to tritium gas in the presence of a suitable catalyst.

E. N-Methylation using Methyl Iodide [³H]: This procedure is usually employed to prepare O-methyl or N-methyl (³H) products by treating appropriate precursors with high specific activity methyl iodide (³H). This method in general allows for higher specific activity, such as for example, about 70-90 Ci/mmol.

Synthetic methods for incorporating activity levels of ¹²⁵I into target molecules include:

A. Sandmeyer and like reactions: This procedure transforms an aryl amine or a heteroaryl amine into a diazonium salt, such as a diazonium tetrafluoroborate salt and subsequently to ¹²⁵I labeled compound using Na¹²⁵I. A represented procedure was reported by Zhu, G-D. and co-workers in *J. Org. Chem.*, 2002, 67, 943-948.

B. Ortho ¹²⁵Iodination of phenols: This procedure allows for the incorporation of ¹²⁵I at the ortho position of a phenol as reported by Collier, T. L. and co-workers in *J. Labelled Compd. Radiopharm.*, 1999, 42, S264-S266.

C. Aryl and heteroaryl bromide exchange with ¹²⁵I: This method is generally a two step process. The first step is the conversion of the aryl or heteroaryl bromide to the corresponding tri-alkyltin intermediate using for example, a Pd catalyzed reaction [i.e. Pd(Ph₃P)₄] or through an aryl or heteroaryl lithium, in the presence of a tri-alkyltinhalide or hexaalkyltin [e.g., (CH₃)₃SnSn(CH₃)₃]. A representative procedure was reported by Le Bas, M.-D. and co-workers in *J. Labelled Compd. Radiopharm.* 2001, 44, S280-S282.

A radiolabeled 5-HT_{2A} serotonin receptor compound of Formula (Ia) can be used in a screening assay to identify/evaluate compounds. In general terms, a newly synthesized or identified compound (i.e., test compound) can be evaluated for its ability to reduce binding of the “radio-labeled compound of Formula (Ia)” to the 5-HT_{2A}-receptor. Accordingly, the ability of a test compound to compete with the “radio-labeled compound of Formula (Ia)” for the binding to the 5-HT_{2A} serotonin receptor directly correlates to its binding affinity.

The labeled compounds of the present invention bind to the 5-HT_{2A} serotonin receptor. In one embodiment the labeled compound has an IC₅₀ less than about 500 μM, in another embodiment the labeled compound has an IC₅₀ less than about 100 μM, in yet another

embodiment the labeled compound has an IC₅₀ less than about 10 μM, in yet another embodiment the labeled compound has an IC₅₀ less than about 1 μM and in still yet another embodiment the labeled inhibitor has an IC₅₀ less than about 0.1 μM.

Other uses of the disclosed receptors and methods will become apparent to those in the
5 art based upon, *inter alia*, a review of this disclosure.

As will be recognized, the steps of the methods of the present invention need not be performed any particular number of times or in any particular sequence. Additional objects, advantages and novel features of this invention will become apparent to those skilled in the art upon examination of the following examples thereof, which are intended to be illustrative and
10 not intended to be limiting.

EXAMPLES

Example 1: Syntheses of compounds of the present invention.

Illustrated syntheses for compounds of the present invention are shown in Figures 1
15 through 5 where the symbols have the same definitions as used throughout this disclosure.

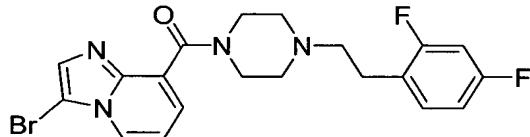
The compounds of the invention and their syntheses are further illustrated by the following examples. The following examples are provided to further define the invention without, however, limiting the invention to the particulars of these examples. The compounds described herein, *supra* and *infra*, are named according to the CS ChemDraw Ultra Version
20 7.0.1, AutoNom version 2.2, or CS ChemDraw Ultra Version 9.0.7. In certain instances common names are used and it is understood that these common names would be recognized by those skilled in the art.

Chemistry: Proton nuclear magnetic resonance (¹H NMR) spectra were recorded on a Bruker Avance-400 equipped with a QNP (Quad Nucleus Probe) or a BBI (Broad Band Inverse) and z-gradient. Chemical shifts are given in parts per million (ppm) with the residual solvent signal used as reference. NMR abbreviations are used as follows: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, t = triplet, td = triplet of doublets, tt = triplet of triplets, q = quartet, m = multiplet, bs = broad singlet, bt = broad triplet. Microwave irradiations were carried out using a Smith Synthesizer™ or an Emrys Optimizer™ (Biotage). Thin-layer chromatography (TLC) was performed on silica gel 60 F₂₅₄ (Merck), preparatory thin-layer chromatography (prep TLC) was preformed on PK6F silica gel 60 Å 1 mm plates (Whatman) and column chromatography was carried out on a silica gel column using Kieselgel 60, 0.063-0.200 mm (Merck). Evaporation was done under reduced pressure on a Büchi rotary evaporator.

35 LCMS spec: HPLC-pumps: LC-10AD VP, Shimadzu Inc.; HPLC system controller: SCL-10A VP, Shimadzu Inc; UV-Detector: SPD-10A VP, Shimadzu Inc; Autosampler: CTC

HTS, PAL, Leap Scientific; Mass spectrometer: API 150EX with Turbo Ion Spray source, AB/MDS Sciex; Software: Analyst 1.2.

Example 1.1: Preparation of (3-Bromoimidazo[1,2-*a*]pyridin-8-yl)(4-(2,4-difluorophenethyl)piperazin-1-yl)methanone (Compound 1).



Step A: Preparation of Imidazo[1,2-*a*]pyridine-8-carboxylic Acid.

2-Aminonicotinic acid (2.0 g, 14.48 mmol) and 2-bromo-1,1-diethoxyethane (2.247 mL, 14.48 mmol) in acetonitrile (10 mL) were heated at 150 °C for 2 h under microwave irradiation.

10 The resulting precipitate was filtered off and washed with acetonitrile and hexane to afford the title compound (2.783 g) as a solid. Exact mass calculated for C₈H₆N₂O₂: 162.0. Found: LCMS *m/z* = 163.1 (M + H)⁺. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.62 (dd, *J* = 6.82, 7.33 Hz, 1H), 8.06 (d, *J* = 2.27 Hz, 1H), 8.36 (d, *J* = 2.02 Hz, 1H), 8.62 (d, *J* = 7.33 Hz, 1H), 9.04 (d, *J* = 6.82 Hz, 1H).

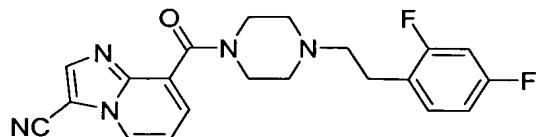
15 **Step B: Preparation of 3-Bromoimidazo[1,2-*a*]pyridine-8-carboxylic Acid.**

Imidazo[1,2-*a*]pyridine-8-carboxylic acid (100 mg, 617 μmol), 1-bromopyrrolidine-2,5-dione (110 mg, 617 μmol) and *N,N*-dimethylformamide (1.5 mL) were stirred at room temperature for 1 h. The resulting precipitate was filtered off and washed with acetonitrile and hexane to afford the title compound as a solid (68 mg). Exact mass calculated for C₈H₅BrN₂O₂: 239.95. Found: LCMS *m/z* (%) = 241.2 ((M + H)⁺, ⁷⁹Br, 100%), 243.2 ((M + H)⁺, ⁸¹Br, 97%). ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.58 (t, *J* = 7.07 Hz, 1H), 8.13 (s, 1H), 8.50 (d, *J* = 7.58 Hz, 1H), 8.84 (d, *J* = 7.07 Hz, 1H).

Step C: Preparation of (3-Bromoimidazo[1,2-*a*]pyridin-8-yl)(4-(2,4-difluorophenethyl)piperazin-1-yl)methanone (Compound 9).

25 1-(2,4-Difluorophenethyl)piperazine hydrochloride (84 mg, 0.28 mmol) was added to a solution of 3-bromoimidazo[1,2-*a*]pyridine-8-carboxylic acid (68 mg, 0.28 mmol), 2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate (HATU) (138 mg, 364 μmol) and triethylamine (117 μL, 840 μmol) in THF (2.7 mL). The reaction mixture was heated at 100 °C under microwave irradiation for 20 min. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC to afford the TFA salt of the title compound as a solid (162 mg). Exact mass calculated for C₂₀H₁₉BrF₂N₄O: 448.1. Found: LCMS *m/z* (%) = 449.1 ((M + H)⁺, ⁷⁹Br, 100%), 451.1 ((M + H)⁺, ⁸¹Br, 97%). ¹H NMR (400 MHz, Acetonitrile-*d*₃) δ 3.01-3.14 (m, 2H), 3.14-3.91 (m, 10H), 6.93-7.01 (m, 2H), 7.34 (dd, *J* = 8.59, 15.16 Hz, 1H), 7.50 (t, *J* = 7.07 Hz, 1H), 7.85 (d, *J* = 7.33 Hz, 1H), 8.02 (s, 1H), 8.56 (d, *J* = 7.07 Hz, 1H).

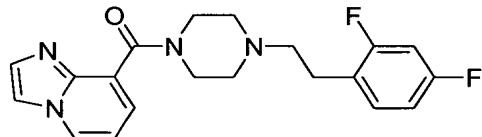
Example 1.2: Preparation of 8-(4-(2,4-Difluorophenethyl)piperazine-1-carbonyl)imidazo[1,2-a]pyridine-3-carbonitrile (Compound 2).



5 (3-Bromoimidazo[1,2-a]pyridin-8-yl)(4-(2,4-difluorophenethyl)piperazin-1-yl)methanone (26 mg, 58 µmol) was added to a solution of dicyanozinc (6.8 mg, 58 µmol), tetrakis(triphenylphosphine)palladium(0) (2.0 mg, 1.736 µmol) and triethylamine (8.1 µL, 58 µmol) in DMF (1.0 mL). The reaction mixture was heated at 120 °C under microwave irradiation for 20 min. The crude mixture was purified by preparative HPLC to afford the TFA salt of the title compound as a solid (5.3 mg). Exact mass calculated for C₂₁H₁₉F₂N₅O: 395.2. Found: LCMS *m/z* = 396.3 (M + H)⁺. ¹H NMR (400 MHz, Acetonitrile-*d*₃) δ 3.10-3.17 (m, 2H), 3.38-3.45 (m, 2H), 3.46-3.58 (m, 4H), 3.72-4.24 (m, 4H), 6.93-6.99 (m, 2H), 7.26 (t, *J* = 7.07 Hz, 1H), 7.31-7.37 (m, 1H), 7.60 (d, *J* = 7.07 Hz, 1H), 8.24 (s, 1H), 8.53 (d, *J* = 7.07 Hz, 1H).

10

15 **Example 1.3: Preparation of (4-(2,4-Difluorophenethyl)piperazin-1-yl)(imidazo[1,2-a]pyridin-8-yl)methanone (Compound 3).**



Step A: Preparation of Imidazo[1,2-a]pyridine-8-carboxylic Acid.

20 To a mixture of 2-aminonicotinic acid (0.6906 g, 5.00 mmol) in acetonitrile (20 mL) was added bromoacetaldehyde dimethyl acetal (0.591 mL, 5.00 mmol). The resulting slurry was heated at 150 °C under microwave irradiation for 2 h. The resulting precipitate was filtered off and washed with acetonitrile and hexane to afford the title compound (0.924 g) as a grey solid. Exact mass calculated for C₈H₆N₂O₂: 162.04. Found: LCMS *m/z* = 163.3 (M + H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.58-7.69 (m, 1H), 8.15 (d, *J* = 2.27 Hz, 1H), 8.50 (dd, *J* = 7.45, 1.14 Hz, 1H), 8.56 (d, *J* = 2.02 Hz, 1H), 9.20 (dd, *J* = 6.69, 1.14 Hz, 1H).

25

Step B: Preparation of *tert*-Butyl 4-(2-(2,4-difluorophenyl)acetyl)piperazine-1-carboxylate.

2-(2,4-Difluorophenyl)acetic acid (5.00 g, 29.1 mmol), 1*H*-benzo[d][1,2,3]triazol-1-ol (4.46 g, 29.1 mmol), *N*¹-((ethylimino)methylene)-*N*³,*N*³-dimethylpropane-1,3-diamine hydrochloride (EDAC) (5.57 g, 29.1 mmol) and triethylamine (4.05 mL, 29.1 mmol) were stirred in DCM (30 mL) for 15 min. *tert*-Butyl piperazine-1-carboxylate (2.71 g, 14.5 mmol) was added and the mixture was stirred at room temperature for 8 h. The reaction was diluted

with DCM (10 mL), washed with 1 N NaOH (5 mL) followed by 1 M citric acid (5 mL). The organic extracts were dried over Na_2SO_4 , filtered and concentrated. The oily residue was purified by preparative HPLC. The fractions containing the desired product were lyophilized to afford material that was neutralized with NaHCO_3 (75 mL) and extracted with EtOAc (2 x 200 mL). The organic extracts were dried over Na_2SO_4 , filtered and concentrated to afford the title compound (1.68 g) as a yellow solid. Exact mass calculated for $\text{C}_{17}\text{H}_{22}\text{F}_2\text{N}_2\text{O}_3$: 340.2. Found: LCMS m/z = 341.3 ($\text{M} + \text{H}$)⁺. ^1H NMR (400 MHz, DMSO- d_6) δ 1.42 (s, 9H), 3.25-3.39 (m, 4H), 3.42-3.48 (m, 2H), 3.49-3.56 (m, 2H), 3.74 (s, 2H), 7.02 (dt, J = 2.7, 8.5 Hz, 1H), 7.18 (dt, J = 2.6, 9.7 Hz, 1H), 7.25-7.33 (m, 1H).

10 **Step C: Preparation of *tert*-Butyl 4-(2,4-Difluorophenethyl)piperazine-1-carboxylate.**

tert-Butyl 4-(2-(2,4-difluorophenyl)acetyl)piperazine-1-carboxylate (1.12 g, 3.30 mmol) was dissolved in THF (8.5 mL) and borane tetrahydrofuran complex (1.0 M, 15.8 mL, 15.8 mmol) was added. The reaction was refluxed at 66 °C. The reaction was quenched slowly with 15 methanol (0.4 mL) dropwise. Then, 0.5 M HCl (10.0 mL) was added and the mixture was extracted with EtOAc (2 x 100 mL). The organic extracts were dried over Na_2SO_4 , filtered and concentrated. The residue was purified by preparative HPLC. The fractions containing the desired product were added to NaHCO_3 (20 mL) and extracted with EtOAc (2 x 100 mL). The organic extracts were dried over Na_2SO_4 , filtered and concentrated to yield the title compound 20 (1.08 g) as a white solid. Exact mass calculated for $\text{C}_{17}\text{H}_{24}\text{F}_2\text{N}_2\text{O}_2$: 326.2. Found: LCMS m/z = 327.1 ($\text{M} + \text{H}$)⁺. ^1H NMR (400 MHz, DMSO- d_6) δ 1.41 (s, 9H), 2.80-2.96 (m, 6H), 3.10-3.03 (m, 2H), 3.50-3.60 (m, 4H), 7.06 (dt, J = 2.6, 8.5 Hz, 1H), 7.22 (dt, J = 2.6, 9.6 Hz, 1H), 7.38-7.46 (m, 1H).

25 **Step D: Preparation of 1-(2,4-Difluorophenethyl)piperazine.**

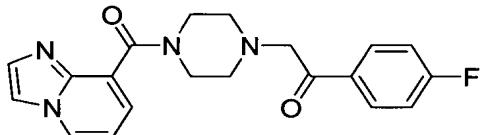
tert-Butyl 4-(2,4-difluorophenethyl)piperazine-1-carboxylate (0.853 g, 2.61 mmol) was dissolved in 4 M HCl in dioxane (10.0 mL) and stirred for 1 h. The reaction was concentrated to afford the hydrochloride salt of the title compound (0.718 g) as a pale solid. Exact mass calculated for $\text{C}_{12}\text{H}_{16}\text{F}_2\text{N}_2$: 226.1. Found: LCMS m/z = 227.2 ($\text{M} + \text{H}$)⁺. ^1H NMR (400 MHz, DMSO- d_6) δ 2.95-3.75 (m, 12H), 6.03-6.80 (bs, 1H), 7.04-7.12 (m, 1H), 7.24 (dt, J = 2.6, 9.6 Hz, 1H), 7.39-7.50 (m, 1H).

30 **Step E: Preparation of (4-(2,4-Difluorophenethyl)piperazin-1-yl)(imidazo[1,2-*a*]pyridin-8-yl)methanone (Compound 3).**

To a solution of imidazo[1,2-*a*]pyridine-8-carboxylic acid (36.6 mg, 226 μmol), 1-(2,4-difluorophenethyl)piperazine hydrochloride (45.0 mg, 150 μmol) and triethylamine (210 μl , 35 1504 μmol) in DMF (0.75 mL) was added 1-propylphosphonic acid anhydride solution (50% in ethyl acetate, 183 μL , 0.301 mmol). The mixture was stirred for 2 h, quenched with water and purified by preparative HPLC/MS. The resultant lyophilate was dissolved in DCM, treated with

MP-carbonate resin (~200 mg). The mixture was stirred for 30 min and filtered to remove the resin. The solvent was removed under reduced pressure to afford the title compound as a white solid (33.0 mg). Exact mass calculated for $C_{20}H_{20}F_2N_4O$: 370.16. Found: LCMS m/z = 371.4 ($M + H$)⁺. 1H NMR (400 MHz, CDCl₃) δ 2.45-2.53 (m, 2H), 2.57-2.64 (m, 2H), 2.64-2.71 (m, 2H), 2.74-2.84 (m, 2H), 3.29-3.43 (m, 2H), 3.85-3.98 (m, 2H), 6.69-6.92 (m, 3H), 7.10-7.21 (m, 1H), 7.23-7.28 (m, 1H), 7.64 (d, J = 1.26 Hz, 1H), 7.69 (d, J = 1.26 Hz, 1H), 8.18 (dd, J = 6.82, 1.26 Hz, 1H).

Example 1.4: Preparation of 1-(4-Fluorophenyl)-2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)ethanone (Compound 4).



Step A: Preparation of *tert*-Butyl 4-(2-(4-Fluorophenyl)-2-oxoethyl)piperazine-1-carboxylate.

tert-Butyl piperazine-1-carboxylate (5.00 g, 26.8 mmol) and 2-bromo-1-(4-fluorophenyl)ethanone (6.99 g, 32.2 mmol) were dissolved in DMF (5 mL) and stirred for 10 min at room temperature. The crude material was purified by column chromatography eluting with a mixture of DCM and MeOH to afford the title compound (3.50 g) as an oil. Exact mass calculated for $C_{17}H_{23}FN_2O_3$: 322.2. Found: LCMS m/z = 323.4 ($M + H$)⁺. 1H NMR (400 MHz, Acetonitrile-*d*₃) δ 1.42 (s, 9H) 2.47 (t, J = 5.0 Hz, 4H), 3.36 (t, J = 5.0 Hz, 4H), 3.77 (s, 2H), 7.20 (t, J = 8.8, 2H), 8.07 (td, J = 2.0, 8.8 Hz, 2H).

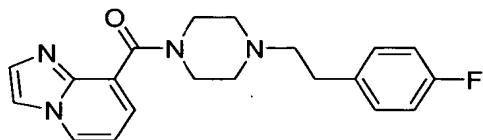
Step B: Preparation of 1-(4-Fluorophenyl)-2-(piperazin-1-yl)ethanone.

The oil from Step A was dissolved in 4 M HCl in dioxane (12 mL) and stirred at 45 °C for 20 min. The solvent was removed under reduced pressure to afford the hydrochloride salt of the title compound (1.80 g) as a white solid. Exact mass calculated for $C_{12}H_{15}FN_2O$: 222.1. Found: LCMS m/z = 223.3 ($M + H$)⁺. 1H NMR (400 MHz, Acetonitrile-*d*₃) δ 3.56 (s, 8H), 5.05 (s, 2H), 7.46 (t, J = 8.8, 2H), 8.10 (td, J = 2.1, 8.8 Hz, 2H).

Step C: Preparation of 1-(4-Fluorophenyl)-2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)ethanone (Compound 4).

The title compound was prepared in a manner similar to that described in Example 1.3, Step E, using imidazo[1,2-a]pyridine-8-carboxylic acid (24.3 mg) and 1-(4-fluorophenyl)-2-(piperazin-1-yl)ethanone hydrochloride (29.5 mg) as starting materials, to afford a brown oil (28.2 mg). Exact mass calculated for $C_{20}H_{19}FN_4O_2$: 366.15. Found: LCMS m/z = 367.3 ($M + H$)⁺.

Example 1.5: Preparation of (4-(4-Fluorophenethyl)piperazin-1-yl)(imidazo[1,2-*a*]pyridin-8-yl)methanone (Compound 5).



Step A: Preparation of *tert*-Butyl 4-(4-fluorophenethyl)piperazine-1-carboxylate.

5 *tert*-Butyl piperazine-1-carboxylate (1.00 g, 5.37 mmol) was dissolved in DMF (20 mL). 1-(2-Bromoethyl)-4-fluorobenzene (2.62 g, 12.9 mmol) and potassium carbonate (2.23 g, 16.1 mmol) were then added to the solution. The reaction was heated for 1 h at 120 °C under microwave irradiation in a heavy-walled sealed tube. The product was purified by HPLC (5-95% acetonitrile/water) to afford the TFA salt of the title compound (1.65 g) as an oil. Exact mass calculated for C₁₇H₂₅FN₂O₂: 308.2. Found: LCMS *m/z* = 309.4 (M + H)⁺.

10 mass calculated for C₁₇H₂₅FN₂O₂: 308.2. Found: LCMS *m/z* = 309.4 (M + H)⁺.

Step B: Preparation of 1-(4-Fluorophenethyl)piperazine.

15 *tert*-Butyl 4-(4-fluorophenethyl)piperazine-1-carboxylate (1.65 g, 5.37 mmol) and 4 M HCl in dioxane (6 mL) were stirred at 43 °C for 1 h. The product was purified by HPLC (5-50% acetonitrile/water) to afford the TFA salt of the title compound (510 mg) as a solid. Exact mass calculated for C₁₂H₁₇FN₂: 208.1. Found: LCMS *m/z* = 209.0 (M + H)⁺.

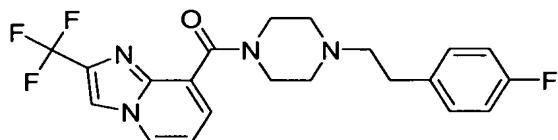
Step C: Preparation of (4-(4-Fluorophenethyl)piperazin-1-yl)(imidazo[1,2-*a*]pyridin-8-yl)methanone (Compound 5).

The title compound was prepared in a manner similar to that described in Example 1.3, Step E, using imidazo[1,2-*a*]pyridine-8-carboxylic acid (24.3 mg) and 1-(4-fluorophenethyl)-piperazine hydrochloride (28.1 mg) as starting materials, to afford an orange solid (34.2 mg). Exact mass calculated for C₂₀H₂₁FN₄O: 352.17. Found: LCMS *m/z* = 353.4 (M + H)⁺. ¹H NMR (400 MHz, CDCl₃) δ 2.43-2.54 (m, 2H), 2.65-2.70 (m, 2H), 2.73-2.81 (m, 2H), 3.36 (t, *J* = 4.80 Hz, 3H), 3.90-3.97 (m, 3H), 6.84 (t, *J* = 6.82 Hz, 1H), 6.92-7.00 (m, 2H), 7.15 (dd, *J* = 8.59, 5.56 Hz, 2H), 7.23-7.26 (m, 1H), 7.63 (d, *J* = 1.01 Hz, 1H), 7.68 (d, *J* = 1.01 Hz, 1H), 8.13-8.22 (m, 1H).

20 mass calculated for C₂₀H₂₁FN₄O: 352.17. Found: LCMS *m/z* = 353.4 (M + H)⁺. ¹H NMR (400 MHz, CDCl₃) δ 2.43-2.54 (m, 2H), 2.65-2.70 (m, 2H), 2.73-2.81 (m, 2H), 3.36 (t, *J* = 4.80 Hz, 3H), 3.90-3.97 (m, 3H), 6.84 (t, *J* = 6.82 Hz, 1H), 6.92-7.00 (m, 2H), 7.15 (dd, *J* = 8.59, 5.56 Hz, 2H), 7.23-7.26 (m, 1H), 7.63 (d, *J* = 1.01 Hz, 1H), 7.68 (d, *J* = 1.01 Hz, 1H), 8.13-8.22 (m, 1H).

25 mass calculated for C₂₀H₂₁FN₄O: 352.17. Found: LCMS *m/z* = 353.4 (M + H)⁺. ¹H NMR (400 MHz, CDCl₃) δ 2.43-2.54 (m, 2H), 2.65-2.70 (m, 2H), 2.73-2.81 (m, 2H), 3.36 (t, *J* = 4.80 Hz, 3H), 3.90-3.97 (m, 3H), 6.84 (t, *J* = 6.82 Hz, 1H), 6.92-7.00 (m, 2H), 7.15 (dd, *J* = 8.59, 5.56 Hz, 2H), 7.23-7.26 (m, 1H), 7.63 (d, *J* = 1.01 Hz, 1H), 7.68 (d, *J* = 1.01 Hz, 1H), 8.13-8.22 (m, 1H).

Example 1.6: Preparation of (4-(4-Fluorophenethyl)piperazin-1-yl)(2-(trifluoromethyl)imidazo[1,2-*a*]pyridin-8-yl)methanone (Compound 6).



30 **Step A: Preparation of Methyl 2-Aminonicotinate**

To a slurry of 2-aminonicotinic acid (2.07 g, 15 mmol) in methanol (45 mL) was added 2.0 M TMS-diazomethane in hexane (15 mL, 30 mmol) and the mixture was stirred for 30 min.

The resulting yellow solution was quenched with acetic acid (10 mL) and concentrated under reduced pressure and azeotroped with hexane. The residue was taken up in MeOH and treated with MP-carbonate resin (10 g, ~30 mmol) for 30 min. The mixture was filtered to remove the resin and the filtrate was concentrated under vacuum. The residue was purified *via* column chromatography (1:9:1:2 EtOAc/hexane) to afford the title compound as a white solid (1.63 g).
5
 ^1H NMR (400 MHz, DMSO-*d*₆) δ 3.81 (s, 3H), 6.62 (dd, *J* = 7.83, 4.55 Hz, 1H), 7.17 (bs, 2H), 8.05 (dd, *J* = 7.83, 2.02 Hz, 1H), 8.21 (dd, *J* = 4.55, 2.02 Hz, 1H).

Step B: Preparation of Methyl 2-Trifluoromethyl-imidazo[1,2-*a*]pyridine-8-carboxylate.

10 To a solution of methyl 2-aminonicotinate (0.304 g) in acetonitrile (10 mL) was added 3-bromo-1,1,1-trifluoroacetone (0.230 mL). The resulting solution was heated to 80 °C for 18 h. The solution was cooled to room temperature and concentrated under reduced pressure. The residue was taken up in water, K₂CO₃ (0.691 g, 5 mmol) was added and the mixture was extracted 3 times with EtOAc. The combined extracts were washed with brine, dried over 15 MgSO₄ and concentrated. The residue was purified *via* column chromatography (1:5:1:1 EtOAc/hexane) to afford the title compound as a white solid (0.148 g). ^1H NMR (400 MHz, CDCl₃) δ 4.05 (s, 3H), 7.03 (*t*, *J* = 7.07 Hz, 1H), 7.99 (s, 1H), 8.10 (dd, *J* = 7.07, 1.26 Hz, 1H), 8.35 (dd, *J* = 6.82, 1.26 Hz, 1H).

20 **Step C: Preparation of 2-Trifluoromethyl-imidazo[1,2-*a*]pyridine-8-carboxylic Acid.**

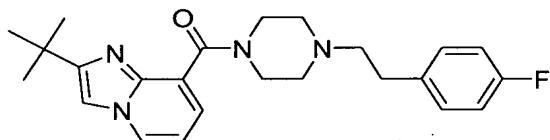
To a solution of methyl 2-trifluoromethyl-imidazo[1,2-*a*]pyridine-8-carboxylate (0.148 g, 0.606 mmol) in 5 mL of H₂O/EtOH (1:2) was added 5 M NaOH (0.195 mL, 0.975 mmol). The solution was heated to reflux for 2 h. After neutralization with 1 M HCl (1.0 mL, 1.0 mmol), the solution was cooled in a freezer overnight. The resulting precipitate was filtered off 25 and washed with EtOH to afford the title compound as a white solid (0.0676 g). ^1H NMR (400 MHz, DMSO-*d*₆) δ 7.18 (*t*, *J* = 6.95 Hz, 1H), 8.03 (dd, *J* = 7.20, 1.14 Hz, 1H), 8.66 (s, 1H), 8.81 (dd, *J* = 6.82, 1.01 Hz, 1H), 13.34 (bs, 1H).

Step D: Preparation of (4-(4-Fluorophenethyl)piperazin-1-yl)(2-(trifluoromethyl)imidazo[1,2-*a*]pyridin-8-yl)methanone (Compound 6).

30 The title compound was prepared in a manner similar to that described in Example 1.3, Step E, using 2-trifluoromethyl-imidazo[1,2-*a*]pyridine-8-carboxylic acid (34.5 mg) and 1-(4-fluorophenethyl)-piperazine hydrochloride (28.2 mg) as starting materials, to afford a clear oil (12.8 mg). Exact mass calculated for C₂₁H₂₀F₄N₄O: 420.16. Found: LCMS *m/z* = 421.3 (M + H)⁺.

35

Example 1.7: Preparation of (2-*tert*-Butylimidazo[1,2-*a*]pyridin-8-yl)(4-(4-fluorophenethyl)piperazin-1-yl)methanone (Compound 7).



Step A: Preparation of Methyl 2-*tert*-Butyl-imidazo[1,2-*a*]pyridine-8-carboxylate.

The title compound was prepared in a manner similar to that described in Example 1.6, Step B, using 1-bromo-3,3-dimethylbutan-2-one (90%, 0.4439 mL) and methyl 2-aminonicotinate (0.304 g) as starting materials, to afford a white solid (0.303 g). ¹H NMR (400 MHz, CDCl₃) δ 1.43 (s, 9H), 4.01 (s, 3H), 6.78 (t, J = 6.95 Hz, 1H), 7.42 (s, 1H), 7.90 (d, J = 7.33 Hz, 1H), 8.22 (d, J = 6.82 Hz, 1H).

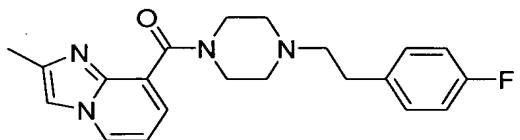
Step B: Preparation of 2-*tert*-Butyl-imidazo[1,2-*a*]pyridine-8-carboxylic Acid.

The title compound was prepared in a manner similar to that described in Example 1.4, Step C, using methyl 2-*tert*-butyl-imidazo[1,2-*a*]pyridine-8-carboxylate (0.303 g) as starting material, to afford a white solid (0.0911 g). ¹H NMR (400 MHz, DMSO-d₆) δ 1.40 (s, 9H), 7.36 (t, J = 6.95 Hz, 1H), 8.14 (s, 1H), 8.21 (d, J = 7.07 Hz, 1H), 8.91 (dd, J = 6.82, 1.01 Hz, 1H).

Step C: Preparation of (2-*tert*-Butylimidazo[1,2-*a*]pyridin-8-yl)(4-(4-fluorophenethyl)piperazin-1-yl)methanone (Compound 7).

The title compound was prepared in a manner similar to that described in Example 1.3, Step E, using 2-*tert*-butyl-imidazo[1,2-*a*]pyridine-8-carboxylic acid (32.7 mg) and 1-(4-fluorophenethyl)-piperazine hydrochloride (28.2 mg) as starting materials, to afford a clear oil (12.8 mg). Exact mass calculated for C₂₄H₂₉FN₄O: 408.23. Found: LCMS m/z = 409.5 (M + H)⁺. ¹H NMR (400 MHz, CDCl₃) δ 1.36 (s, 9H), 2.57 (bs, 2H), 2.59-2.66 (m, 2H), 2.70 (t, J = 4.93 Hz, 2H), 2.76-2.84 (m, 2H), 3.30-3.38 (m, 2H), 3.93 (bs, 2H), 6.74 (t, J = 6.95 Hz, 1H), 6.93-7.02 (m, 2H), 7.10-7.20 (m, 2H), 7.20-7.25 (m, 1H), 7.36 (s, 1H), 8.08 (dd, J = 6.69, 1.14 Hz, 1H).

Example 1.8: Preparation of (4-(4-Fluorophenethyl)piperazin-1-yl)(2-methylimidazo[1,2-*a*]pyridin-8-yl)methanone (Compound 8).



Step A: Preparation of Methyl 2-Methyl-imidazo[1,2-*a*]pyridine-8-carboxylate.

The title compound was prepared in a manner similar to that described in Example 1.6, Step B, using 1-bromo-2,2-dimethoxypropane (0.271 mL) and methyl 2-aminonicotinate (0.304 g) as starting materials, to afford a beige solid (0.102 g). ¹H NMR (400 MHz, CDCl₃) δ 2.54 (s, 3H), 4.04 (s, 3H), 6.82 (t, J = 6.95 Hz, 1H), 7.43 (s, 1H), 7.93 (dd, J = 7.33, 1.26 Hz, 1H), 8.22 (dd, J = 6.57, 1.26 Hz, 1H).

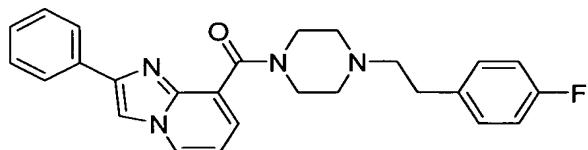
Step B: Preparation of 2-Methyl-imidazo[1,2-*a*]pyridine-8-carboxylic Acid, Sodium Salt.

To a solution of methyl 2-methyl-imidazo[1,2-*a*]pyridine-8-carboxylate (0.100 g, 0.525 mmol) in 6 mL of H₂O/EtOH (1:2) was added 1 M NaOH (578 μL, 578 μmol). The solution was heated to reflux for 1 h. The solution was cooled to room temperature and concentrated under reduced pressure to afford the title compound as a white solid (0.104 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.33 (s, 3H), 4.14 (bs, 1H), 6.77 (t, *J* = 6.82 Hz, 1H), 7.56 (dd, *J* = 7.07, 1.52 Hz, 1H), 7.62 (s, 1H), 8.38 (dd, *J* = 6.57, 1.26 Hz, 1H).

Step C: Preparation of (4-(4-Fluorophenethyl)piperazin-1-yl)(2-methylimidazo[1,2-*a*]pyridin-8-yl)methanone (Compound 8).

The title compound was prepared in a manner similar to that described in Example 1.3, Step E, using 2-methyl-imidazo[1,2-*a*]pyridine-8-carboxylic acid, sodium salt (26.4 mg) and 1-(4-fluorophenethyl)-piperazine hydrochloride (28.1 mg) as starting materials, to afford a white solid (27.9 mg). Exact mass calculated for C₂₁H₂₃FN₄O: 366.19. Found: LCMS *m/z* = 367.5 (M + H)⁺. ¹H NMR (400 MHz, CDCl₃) δ 2.46 (s, 3H), 2.58-2.64 (m, 4H), 2.67 (bs, 2H), 2.73-2.82 (m, 2H), 3.38 (t, *J* = 4.80 Hz, 2H), 3.93 (bs, 2H), 6.77 (t, *J* = 6.82 Hz, 1H), 6.92-7.01 (m, 2H), 7.10-7.21 (m, 3H), 7.38 (s, 1H), 8.07 (dd, *J* = 6.69, 1.14 Hz, 1H).

Example 1.9: Preparation of (4-(4-Fluorophenethyl)piperazin-1-yl)(2-phenylimidazo[1,2-*a*]pyridin-8-yl)methanone (Compound 9).



Step A: Preparation of Methyl 2-Phenyl-imidazo[1,2-*a*]pyridine-8-carboxylate.

The title compound was prepared in a manner similar to that described in Example 1.6, Step B, using bromoacetophenone (0.398 g) and methyl 2-aminonicotinate (0.304 g) as starting materials, to afford a white solid (0.310 g). ¹H NMR (400 MHz, CDCl₃) δ 4.08 (s, 3H), 6.88 (t, *J* = 6.95 Hz, 1H), 7.32-7.38 (m, 1H), 7.41-7.48 (m, 2H), 7.96 (s, 1H), 7.99 (dd, *J* = 7.07, 1.26 Hz, 1H), 8.01-8.05 (m, 2H), 8.32 (dd, *J* = 6.57, 1.26 Hz, 1H).

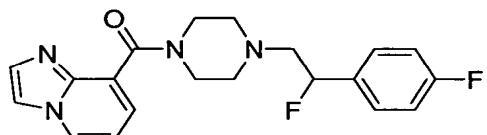
Step B: Preparation of 2-Phenyl-imidazo[1,2-*a*]pyridine-8-carboxylic Acid, Sodium Salt.

The title compound was prepared in a manner similar to that described in Example 1.8, Step B, using methyl 2-phenyl-imidazo[1,2-*a*]pyridine-8-carboxylate (0.310 g) as starting material, to afford a white solid (0.320 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.13 (t, *J* = 6.95 Hz, 1H), 7.34-7.42 (m, 1H), 7.50 (t, *J* = 7.58 Hz, 2H), 7.93-8.03 (m, 3H), 8.61 (s, 1H), 8.82 (dd, *J* = 6.69, 1.14 Hz, 1H).

Step C: Preparation of (4-(4-Fluorophenethyl)piperazin-1-yl)(2-phenylimidazo[1,2-a]pyridin-8-yl)methanone (Compound 9).

The title compound was prepared in a manner similar to that described in Example 1.3, Step E, using 2-phenyl-H-imidazo[1,2-a]pyridine-8-carboxylic acid, sodium salt (28.6 mg) and 1-(4-fluorophenethyl)-piperazine hydrochloride (28.1 mg) as starting materials, to afford a white solid (37.8 mg). Exact mass calculated for $C_{26}H_{25}FN_4O$: 428.20. Found: LCMS m/z = 429.3 ($M + H^+$). 1H NMR (400 MHz, $CDCl_3$) δ 2.58 (bs, 2H), 2.63-2.69 (m, J = 8.34 Hz, 2H), 2.74 (bs, 2H), 2.77-2.85 (m, 2H), 3.44 (bs, 2H), 3.97 (bs, 2H), 6.84 (t, J = 6.82 Hz, 1H), 6.93-7.03 (m, 2H), 7.10-7.20 (m, 2H), 7.29-7.37 (m, 2H), 7.39-7.47 (m, 2H), 7.92 (s, 1H), 7.96-8.02 (m, 2H), 8.18 (dd, J = 6.82, 1.26 Hz, 1H).

Example 1.10: Preparation of (4-(2-Fluoro-2-(4-fluorophenyl)ethyl)piperazin-1-yl)(imidazo[1,2-a]pyridin-8-yl)methanone (Compound 10).



Step A: Preparation of *tert*-Butyl 4-(1-Fluoro-2-(4-fluorophenyl)ethyl)piperazine-1-carboxylate.

1-(2-Bromo-1-fluoroethyl)-4-fluorobenzene (334 mg, 1.511 mmol), prepared as described by Schlosser *et al.*, *Tetrahedron* 60, 2004, 7731-7742, was dissolved in DMF (1.5 mL). *tert*-Butyl piperazine-1-carboxylate (310 mg, 1.662 mmol), potassium hydrogen carbonate (151 mg, 1.511 mmol) and potassium iodide (25.08 mg, 0.151 mmol) were added and the mixture was stirred at 80 °C overnight. The reaction mixture was cooled to room temperature, diluted with water and extracted twice with dichloromethane. The combined extracts were dried with sodium sulfate, filtered and concentrated to dryness. The crude product was purified by flash chromatography on silica gel (ethyl acetate:hexanes, 1:1) to afford the title compound as a white solid (142 mg, 28.8%). Exact mass calculated for $C_{17}H_{24}F_2N_2O_2$: 326.18. Found: LCMS m/z = 327.4 ($M + H^+$). 1H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.62 (ddd, J = 33.3, 14.3, 2.8 Hz, 1H) 2.62-2.45 (m, 4H), 2.90 (ddd, J = 17.3, 14.3, 8.6 Hz, 1H), 3.46 (t, J = 4.8 Hz, 4H), 5.63 (ddd, J = 40.5, 8.6, 2.5 Hz, 1H), 7.07 (t, J = 8.6 Hz, 2H), 7.32 (dd, J = 8.5, 5.6 Hz, 2H).

Step B: Preparation of 1-(2-Fluoro-2-(4-fluorophenyl)ethyl)piperazine Dihydrochloride Salt.

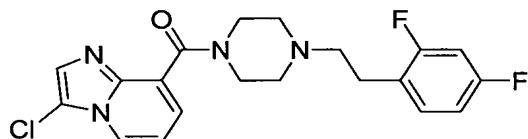
Acetyl chloride (0.152 mL, 2.145 mmol) was added dropwise to ice cold methanol (4 mL) while stirring vigorously. After the addition was complete, the ice bath was removed and the solution was stirred at room temperature. After 15 min, the solution was transferred to a flask containing *tert*-butyl 4-(2-fluoro-2-(4-fluorophenyl)ethyl)piperazine-1-carboxylate (140 mg, 0.429 mmol) and the mixture was stirred at room temperature for 4 h. The precipitate was

isolated by filtration, washed with ice-cold methanol and ether and dried under reduced pressure over KOH to afford the title compound as a white solid (104 mg, 81%). Exact mass calculated for C₁₂H₁₆F₂N₂: 226.13. Found: LCMS *m/z* = 227.4 (M + H)⁺. ¹H NMR (400 MHz, D₂O) δ 3.35 (ddd, *J* = 35.6, 14.3, 2.2 Hz, 1H), 3.56-343 (m, 8H), 3.65 (ddd, *J* = 14.3, 13.3, 10.3 Hz, 1H), 5.99 (ddd, *J* = 49.1, 10.3, 1.8 Hz, 1H), 7.08 (t, *J* = 8.9 Hz, 2H), 7.35 (dd, *J* = 7.7, 5.5 Hz, 2H).

Step C: Preparation of (4-(2-Fluoro-2-(4-fluorophenyl)ethyl)piperazin-1-yl)(imidazo[1,2-*a*]pyridin-8-yl)methanone (Compound 10).

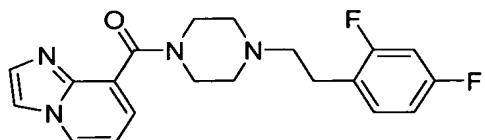
The title compound was prepared in a manner similar to that described in Example 1.3, Step E, using imidazo[1,2-*a*]pyridine-8-carboxylic acid (24.3 mg) and 1-(2-fluoro-2-(4-fluorophenyl)ethyl)piperazine hydrochloride (29.9 mg) to afford a white solid (31.0 mg). Exact mass calculated for C₂₀H₂₀F₂N₄O: 370.16. Found: LCMS *m/z* = 370.9 (M + H)⁺.

Example 1.11: Preparation of (3-Chloroimidazo[1,2-*a*]pyridin-8-yl)(4-(2,4-difluorophenethyl)piperazin-1-yl)methanone (Compound 11).



(4-(2,4-Difluorophenethyl)piperazin-1-yl)(imidazo[1,2-*a*]pyridin-8-yl)methanone (500 mg, 1.350 mmol), 1-chloropyrrolidine-2,5-dione (216 mg, 1.620 mmol) and 2-propanol (10 mL) were stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC to afford the TFA salt of the title compound as a solid (348 mg). Exact mass calculated for C₂₀H₁₉ClF₂N₄O: 404.1. Found: LCMS *m/z* (%) = 405.3 ((M + H)⁺, ³⁵Cl, 100%), 407.3 ((M + H)⁺, ³⁷Cl, 32%). ¹H NMR (400 MHz, Acetonitrile-*d*₃) δ 3.10-3.17 (m, 2H), 3.38-3.45 (m, 2H), 3.46-3.58 (m, 4H), 3.72-4.24 (m, 4H), 6.93-7.00 (m, 2H), 7.30-7.36 (m, 1H), 7.37-7.41 (m, 1H), 7.71 (d, *J* = 7.07 Hz, 1H), 7.89 (s, 1H), 8.47 (d, *J* = 7.07 Hz, 1H).

Example 1.12: Preparation of (4-(2,4-Difluorophenethyl)piperazin-1-yl)(imidazo[1,2-*a*]pyridin-8-yl)methanone Hydrochloride Salt (Compound 3).



Step A: Preparation of Imidazo[1,2-*a*]pyridine-8-carboxylic Acid Hydrochloride.

To a mixture of 2-aminonicotinic acid, (152.19 g, 1.102 mol) was added chloroacetaldehyde (45 wt % in water, 230 mL and 1.31 mol). The resulting slurry was heated

to 60 °C in an oil bath with efficient stirring. The slurry gradually became homogenous and a strong exothermic reaction increasing the temperature by 20-22 °C was noticed. The heating was discontinued and the reaction mixture was allowed to cool to room temperature. Solids started separating out, the resulting slurry was diluted with isopropanol (870 mL) and the mixture was stirred at room temperature for 1 h followed by cooling to 0-10 °C for an additional 1 h. The solids were filtered off and washed with isopropanol (435 mL) and heptanes (2 x 140 mL) and dried at 40 °C in vacuum oven to afford the title compound (200.3 g, 92%) as a pale tan solid. Exact mass calculated for C₈H₆N₂O₂: 162.04. Found: LCMS *m/z* = 163.0 (M + H)⁺. ¹H NMR (400 MHz, D₂O) δ 7.53 (t, *J* = 7.0 Hz, 1H), 7.96 (d, *J* = 1 Hz, 1H), 8.25 (d, *J* = 1 Hz, 1H), 8.45 (d, *J* = 7.4 Hz, 1H), 8.93 (d, *J* = 6.7 Hz, 1H).

Step B: Preparation of Imidazo[1,2-*a*]pyridine-2-carbonyl chloride Hydrochloride.

Method 1: To imidazo[1,2-*a*]pyridine-8-carboxylic acid hydrochloride (10.0 g, 50.4 mmol), thionyl chloride (98 g, 60 mL, 822 mmol) was added. To the resulting mixture *N,N*-dimethylformamide (1.6 mL) was added. Gas evolution was noticed and the reaction mixture was heated to 50 °C overnight (18 h). The reaction mixture was then cooled to room temperature and the product was filtered and washed with isopropyl acetate (40 mL) followed by 10% isopropanol in isopropyl acetate (40 mL). The white solid thus obtained was dried under reduced pressure to afford the title compound (10.2 g, 93%). The compound was used without further purification in Step E.

Method 2: To imidazo[1,2-*a*]pyridine-8-carboxylic acid hydrochloride (15.0 g, 76 mmol), toluene (80 mL) was added followed by thionyl chloride (17.4 g, 146 mmol). To the resulting mixture, *N,N*-dimethylformamide (1.15 mL) was added. Gas evolution was noticed and the mixture was stirred at ambient temperature for 30 min and then was heated to 50 °C overnight (18 h). The reaction mixture was then cooled to room temperature for 30 min and the product was filtered and washed with isopropyl acetate (40 mL) followed by ethyl acetate (40 mL). The white solid was dried under reduced pressure to afford the title compound (13.4 g, 82%). The compound was used without further purification in step E. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.69 (t, *J* = 6.98 Hz, 1H), 8.18 (d, *J* = 1 Hz, 1H), 8.53 (m, 1H), 8.65 (d, *J* = 1 Hz, 1H), 9.27 (d, *J* = 6.7 Hz, 1H), 13.9-14.4 (br, 1H).

Step C: Preparation of *tert*-Butyl 4-(2-(2,4-Difluorophenyl) acetyl)piperazine-1-carboxylate.

Method 1: 2-(2,4-Difluorophenyl)acetic acid (100 g, 0.58 mol), boric acid (3.63g, 58.7 mmol) and phenylboronic acid (3.58 g, 29.36 mmol) were dissolved in toluene (700 mL). After 15 min, *tert*-butyl piperazine-1-carboxylate (121 g, 0.65 mol) was added portionwise and the resulting mixture was heated to 110 °C with stirring. The reaction flask was equipped with a Dean-Stark apparatus to remove water. The mixture was maintained under gentle reflux for 48 h until the theoretical amount of water was collected. After completion of reaction, the mixture

was cooled to 20-25 °C and concentrated using a rotary evaporator. The residue was diluted with ethyl acetate (500 mL) and washed with water (75 mL). The organic extracts were dried over sodium sulfate (Na_2SO_4), filtered and concentrated to afford a sticky solid, which was triturated with ethyl acetate/heptanes (2:1, 350 mL). The solid thus formed was filtered and dried to afford the title compound (146.5 g, 74%) as a pale yellow solid. Exact mass calculated for $\text{C}_{17}\text{H}_{22}\text{F}_2\text{N}_2\text{O}_3$: 340.16; Found: LCMS m/z = 341.3 ($\text{M} + \text{H}$)⁺. ^1H NMR (400 MHz, DMSO- d_6) δ 1.42 (s, 9H), 3.25-3.39 (m, 4H), 3.42-3.48 (m, 2H), 3.49-3.56 (m, 2H), 3.74 (s, 2H), 7.02 (dt, J = 2.7, 8.5 Hz, 1H), 7.18 (dt, J = 2.6, 9.7 Hz, 1H), 7.25-7.33 (m, 1H).

Method 2: 2-(2,4-Difluorophenyl)acetic acid (202.6 g, 1.18 mol), was dissolved in acetonitrile (1.8 L). Carbonyldiimidazole (188.4 g, 1.16 mol) was added portionwise at room temperature. There was gas evolution due to the liberation of carbon dioxide. After the addition was completed, the mixture was heated to 60 °C with stirring for 4 h. The active intermediate thus formed was cooled to room temperature. *tert*-Butyl piperazine-1-carboxylate (219 g, 1.175 mol) was added and the mixture heated to 60 °C with stirring for 4 h. The reaction was monitored by LC/MS for consumption of the starting material. The crude reaction mixture was cooled to 20-25 °C and the solvent was removed using a rotary evaporator. The pale yellow solid residue was suspended in 5% sodium hydroxide (1 L), mixed well for 20 min and filtered. The solid collected was then washed with water (1 L) and dried in a vacuum oven at 50-55 °C overnight to afford the title compound (329 g, 82%).

20 Step D: Preparation of 1-(2,4-Difluorophenethyl)piperazine Hydrochloride.

tert-Butyl 4-(2-(2,4-difluorophenyl)acetyl)piperazine-1-carboxylate (101.2 g, 297 mmol) was dissolved in THF (800 mL) and borane tetrahydrofuran complex (1.0 M, 666 mL, 666 mmol) was added. The addition was carried out carefully while keeping the temperature below 20 °C. The reaction mixture was then heated to 50-55 °C for 2 h. The reaction was monitored by LC/MS for consumption of the starting material. The crude mixture was quenched carefully over 1 h with ethyl acetate (150 mL) followed by addition of methanol (150 mL). After the gas evolution had subsided, about two thirds of the solvent was removed using a rotary evaporator and the remaining solution was diluted with isopropyl acetate (800 mL). Sodium hydroxide (25% solution, 160 g) was added dropwise while the temperature was maintained below 25 °C. After the addition was complete the reaction mixture was then heated to 55-60 °C for 2 h and then gradually cooled to room temperature. The layers were separated and the basic aqueous layer was discarded. The organic layer was dried over sodium sulfate (50 g) and filtered. The solvent was removed using a rotary evaporator. The residual oil was dissolved in isopropanol (800 mL) and HCl (~10-11 N, 79 mL) was added slowly over a period of 30 minutes. After completion of the addition, the mixture was heated to 65-70 °C for 4 h and was then cooled to 0-10 °C in an ice-bath for 2 h. The precipitate was filtered, washed with isopropanol (100 ml) and dried to afford the title compound as a white solid (75.6 g, 85%).

Exact mass calculated for C₁₂H₁₆F₂N₂: 226.13; Found: LCMS *m/z* = 227.2 (M + H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.95-3.75 (m, 12H), 6.03-6.80 (br, 1H), 7.04-7.12 (m, 1H), 7.24 (dt, *J* = 2.6, 9.6 Hz, 1H), 7.39-7.50 (m, 1H).

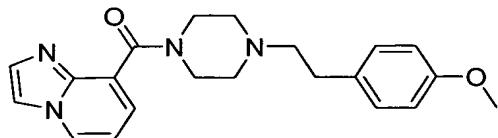
5 **Step E: Preparation of (4-(2,4-Difluorophenethyl)piperazin-1-yl)(imidazo[1,2-
a]pyridin-8-yl)methanone.**

1-(2,4-Difluorophenethyl) piperazine hydrochloride (13.0 g, 43.45 mmol), was suspended in acetonitrile (130 mL). To this solution diisopropylethylamine (23.1 g, 179 mmol) was added with cooling in an ice-bath to keep the temperature below 20 °C during addition. The reaction mixture slowly became homogenous. To the reaction mixture, imidazo[1,2-
10 a]pyridine-8-carbonyl chloride hydrochloride (10.2 g, 47.0 mmol) was added. The mixture was stirred and the progress of the reaction was monitored by LC/MS. A solid precipitate was formed quickly. The mixture was stirred at ambient for 30 min, slowly heated to 45-50 °C and then stirred for 3 h. LC/MS of the reaction mixture showed that the reaction was 80% complete and therefore additional portions of the acid chloride (2.9 g, 9.2 mmol) were added. The
15 mixture was stirred at 45-50 °C overnight (18 h). The solvent was removed using a rotary evaporator and the residue was dissolved in water (75 mL). The pH of the solution was adjusted to 10-11 with 25% sodium hydroxide. An oil layer was separated and extracted with isopropyl acetate (2 x 40 mL). The combined organic phases were washed with water (25 mL), dried over sodium sulfate (10 g) and filtered. The filtrate was concentrated to afford the crude freebase of
20 the title compound (13.7 g, 85% yield) as a tan solid. Exact mass calculated for C₂₀H₂₀F₂N₄O: 370.16; Found: LCMS *m/z* = 370.9 (M + H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.38 (t, *J* = 1 Hz, 2H), 2.52 (m, 4H), 2.74 (t, *J* = 1 Hz, 2H), 3.13 (t, *J* = 1 Hz, 2H), 3.67 (t, *J* = 1 Hz, 2H), 6.93 (t, *J* = 7Hz, 1H), 6.99 (dt, *J* = 7Hz, 1Hz, 1H), 7.14(dt, *J* = 6Hz, 1Hz, 1H), 7.21 (d, *J* = 6Hz, 1H), 7.38 (q, *J* = 6Hz, 1 H), 7.61 (m, , 1 H), 7.95 (m, 1 H), 8.62 (d, *J* = 6Hz, 1 H).

25 **Step F: Preparation of (4-(2,4-Difluorophenethyl)piperazin-1-yl)(imidazo[1,2-
a]pyridin-8-yl)methanone Hydrochloride.**

(4-(2,4-Difluorophenethyl)piperazin-1-yl)(imidazo[1,2-a]pyridin-8-yl)methanone (10.2 g, 27.5 mmol) prepared in step E was dissolved in isopropanol (110 mL). Hydrochloric acid (10 N, 6.05 mL) was added, the mixture was heated to 40 °C and stirred for 1 h. A solid precipitate was formed. The mixture was allowed to cool to room temperature and stirred at 20-25 °C overnight. The solid was filtered, washed with isopropanol (30 mL) and dried in a vacuum oven at 60 °C overnight to afford the title compound (10.6 g, 86%). Exact mass calculated for C₂₀H₂₀F₂N₄O: 370.16; Found: LCMS *m/z* = 371.4 (M + H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.14 (m, 2H), 3.22 (m, 2H), 3.69-3.78 (br, 8H), 4.45-4.77 (br, 1H), 7.09 (dt, *J* = 1, 8 Hz, 1H), 7.25 (dt, *J* = 1, 8 Hz, 1H), 7.44 (q, *J* = 8 Hz, 1H), 7.55 (t, *J* = 8 Hz, 1H), 7.99 (d, *J* = 7 Hz, 1H), 8.21 (s, 1H), 8.50 (d, *J* = 1 Hz, 1H), 9.01 (d, *J* = 8 Hz, 1H), 12.05-12.25 (br s, 1H).

Example 1.13: Preparation of Imidazo[1,2-*a*]pyridin-8-yl(4-(4-methoxyphenethyl)piperazin-1-yl)methanone (Compound 12).



5 **Step A: Preparation of *tert*-Butyl 4-(imidazo[1,2-*a*]pyridine-8-carbonyl)piperazine-1-carboxylate.**

Imidazo[1,2-*a*]pyridine-8-carbonyl chloride (2.00 g, 11.07 mmol) was added to a solution of *tert*-butyl piperazine-1-carboxylate (2.269 g, 12.18 mmol) and triethylamine (5.40 mL, 38.8 mmol) in THF (15 mL). The solution was stirred at room temperature for 30 min. The solvent was removed under reduced pressure to afford the title compound (1.25 g) as a solid. Exact mass calculated for C₁₇H₂₂N₄O₃ 330.2, found 331.2 (M + H)⁺.

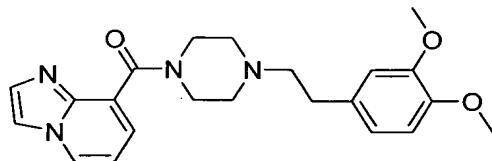
10 **Step B: Preparation of Imidazo[1,2-*a*]pyridin-8-yl(piperazin-1-yl)methanone Hydrochloride Salt.**

15 *tert*-Butyl 4-(imidazo[1,2-*a*]pyridine-8-carbonyl)piperazine-1-carboxylate (1.25 g, 3.78 mmol) and 4 M HCl in dioxane (15 mL) were stirred at 43 °C for 30 min. The precipitate was filtered, washed with hexane and dried under reduced pressure to afford the HCl salt of the title compound as a solid (980 mg). Exact mass calculated for C₁₂H₁₄N₄O 230.1. Found 231.1 (M + H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.02-3.15 (m, 2H) 3.57-3.71 (m, 2H), 3.88-4.03 (m, 2H), 4.15-4.68 (m, 2H), 7.56 (t, *J* = 7.07 Hz, 1H), 8.03 (d, *J* = 7.07 Hz, 1H), 8.25 (d, *J* = 2.02 Hz, 1H), 8.50 (d, *J* = 2.0 Hz, 1H), 9.02 (d, *J* = 6.57 Hz, 1H).

20 **Step C: Preparation of Imidazo[1,2-*a*]pyridin-8-yl(4-(4-methoxyphenethyl)piperazin-1-yl)methanone (Compound 12).**

25 1-(2-Bromoethyl)-4-methoxybenzene (48 mg, 187 μmol) was added to a solution of imidazo[1,2-*a*]pyridin-8-yl(piperazin-1-yl)methanone hydrochloride (50 mg, 187 μmol) and potassium carbonate (78 mg, 562 μmol) in DMF (3.0 mL). The mixture was heated at 120 °C for 20 min under microwave irradiation. The residue was purified by preparative HPLC to give a solid (TFA salt) in 15.7% yield (14.1 mg). Exact mass calculated for C₂₁H₂₄N₄O₂: 364.2. Found: LCMS *m/z* = 365.4 (M + H)⁺. ¹H NMR (400 MHz, Acetonitrile-*d*₃) δ 2.97-3.02 (m, 2H) 3.23-3.29 (m, 2H), 3.30-3.75 (m, 8H), 3.76 (s, 3H), 6.86-6.90 (m, 2H), 7.15-7.19 (m, 2H), 7.43 (t, *J* = 7.1 Hz, 1H), 7.84 (d, *J* = 7.1 Hz, 1H), 7.93 (d, *J* = 2.0 Hz, 1H), 8.06 (d, *J* = 2.0 Hz, 1H), 8.64 (dd, *J* = 0.6, 6.8 Hz, 1H).

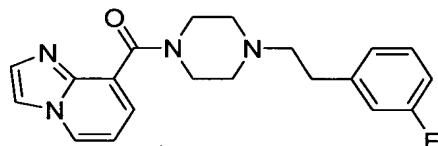
Example 1.14: Preparation of (4-(3,4-Dimethoxyphenethyl)piperazin-1-yl)(imidazo[1,2-*a*]pyridin-8-yl)methanone (Compound 13).



The title compound was prepared in a manner similar to that described in Example 1.13, step C, using imidazo[1,2-a]pyridin-8-yl(piperazin-1-yl)methanone hydrochloride (50 mg, 187 μmol) and 4-(2-bromoethyl)-1,2-dimethoxybenzene (55 mg, 225 μmol) as starting materials, to afford the TFA salt as a solid (8.7 mg). Exact mass calculated for $C_{22}H_{26}N_4O_3$: 394.2. Found: LCMS m/z = 395.4 ($M + H$)⁺. 1H NMR (400 MHz, Acetonitrile- d_3) δ 2.97-3.02 (m, 2H), 3.26-3.31 (m, 2H), 3.30-3.75 (m, 8H), 3.76 (s, 3H), 3.79 (s, 3H), 6.75-6.79 (dd, J = 2.0, 8.1 Hz, 1H), 6.84-6.89 (m, 2H), 7.41 (t, J = 7.0 Hz, 1H), 7.82 (d, J = 7.3 Hz, 1H), 7.93 (d, J = 2.0 Hz, 1H), 8.05 (d, J = 2.0 Hz, 1H), 8.64 (d, J = 6.8 Hz, 1H).

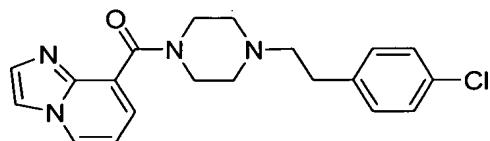
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Example 1.15: Preparation of (4-(3-Fluorophenethyl)piperazin-1-yl)(imidazo[1,2-a]pyridin-8-yl)methanone (Compound 14).



The title compound was prepared in a manner similar to that described in Example 1.13, step C, using imidazo[1,2-a]pyridin-8-yl(piperazin-1-yl)methanone hydrochloride (50 mg, 187 μmol) and 1-(2-bromoethyl)-3-fluorobenzene (46 mg, 225 μmol) as starting materials, to afford the TFA salt as a solid (10.5 mg). Exact mass calculated for $C_{20}H_{21}FN_4O$: 352.2. Found: LCMS m/z = 353.4 ($M + H$)⁺. 1H NMR (400 MHz, Acetonitrile- d_3) δ 3.07-3.12 (m, 2H), 3.28-3.33 (m, 2H), 3.35-3.75 (m, 8H), 6.98-7.11 (m, 3H), 7.34 (t, J = 8.1 Hz, 1H), 7.40 (t, J = 8.1 Hz, 1H), 7.80 (dd, J = 1.0 Hz, 7.2 Hz, 1H), 7.92 (d, J = 2.0 Hz, 1H), 8.05 (d, J = 2.0 Hz, 1H), 8.64 (dd, J = 1.0 Hz, 6.8 Hz, 1H).

Example 1.16: Preparation of (4-(4-Chlorophenethyl)piperazin-1-yl)(imidazo[1,2-a]pyridin-8-yl)methanone (Compound 15).



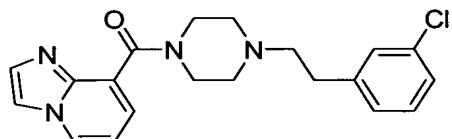
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The title compound was prepared in a manner similar to that described in Example 1.13, step C, using imidazo[1,2-a]pyridin-8-yl(piperazin-1-yl)methanone hydrochloride (50 mg, 187 μmol) and 1-(2-bromoethyl)-4-chlorobenzene (49 mg, 225 μmol) as starting materials, to afford the TFA salt as a solid (14.9 mg). Exact mass calculated for $C_{20}H_{21}ClN_4O$: 368.1.

Found: LCMS m/z (%) = 369.1 ((M + H)⁺, ³⁵Cl, 100%), 371.1 ((M + H)⁺, ³⁷Cl, 33%). ¹H NMR (400 MHz, Acetonitrile-*d*₃) δ 3.06-3.12 (m, 2H) 3.25-3.31 (m, 2H), 3.35-3.80 (m, 8H), 7.24-7.28 (m, 2H), 7.32-7.36 (m, 2H), 7.41 (t, *J* = 7.1 Hz, 1H), 7.81 (dd, *J* = 1.0 Hz, 7.2 Hz, 1H), 7.92 (d, *J* = 2.0 Hz, 1H), 8.05 (d, *J* = 2.0 Hz, 1H), 8.63 (dd, *J* = 1.0 Hz, 6.8 Hz, 1H).

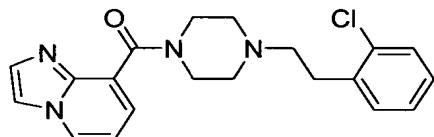
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Example 1.17: Preparation of (4-(3-Chlorophenethyl)piperazin-1-yl)(imidazo[1,2-*a*]pyridin-8-yl)methanone (Compound 16).



The title compound was prepared in a manner similar to that described in Example 1.13, 10 step C, using imidazo[1,2-*a*]pyridin-8-yl(piperazin-1-yl)methanone hydrochloride (50 mg, 187 μ mol) and 1-(2-bromoethyl)-3-chlorobenzene (49 mg, 225 μ mol) as starting materials, to afford the TFA salt as a solid (12.6 mg). Exact mass calculated for C₂₀H₂₁ClN₄O: 368.1. Found: LCMS m/z (%) = 369.1 ((M + H)⁺, ³⁵Cl, 100%), 371.1 ((M + H)⁺, ³⁷Cl, 33%). ¹H NMR (400 MHz, Acetonitrile-*d*₃) δ 3.06-3.11 (m, 2H) 3.28-3.34 (m, 2H), 3.35-3.90 (m, 8H), 7.19-7.23 (m, 1H), 7.26-7.35 (m, 3H), 7.42 (t, *J* = 6.9 Hz, 1H), 7.84 (dd, *J* = 1.0 Hz, 7.2 Hz, 1H), 7.93 (d, *J* = 2.0 Hz, 1H), 8.06 (d, *J* = 2.0 Hz, 1H), 8.64 (dd, *J* = 1.0, 6.8 Hz, 1H).

Example 1.18: Preparation of (4-(2-Chlorophenethyl)piperazin-1-yl)(imidazo[1,2-*a*]pyridin-8-yl)methanone (Compound 17).

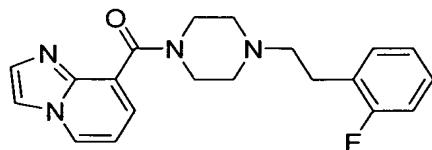


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The title compound was prepared in a manner similar to that described in Example 1.13, step C, using imidazo[1,2-*a*]pyridin-8-yl(piperazin-1-yl)methanone hydrochloride (50 mg, 187 μ mol) and 1-(2-bromoethyl)-2-chlorobenzene (49 mg, 225 μ mol) as starting materials, to afford the TFA salt as a solid (11.8 mg). Exact mass calculated for C₂₀H₂₁ClN₄O: 368.1. Found: LCMS m/z (%) = 369.1 ((M + H)⁺, ³⁵Cl, 100%), 371.1 ((M + H)⁺, ³⁷Cl, 33%). ¹H NMR (400 MHz, Acetonitrile-*d*₃) δ 3.25 (m, 4H), 3.30-3.90 (m, 8H), 7.26-7.31 (m, 2H), 7.33-7.37 (m, 1H), 7.39-7.44 (m, 2H), 7.81 (dd, *J* = 1.0, 7.2 Hz, 1H), 7.93 (d, *J* = 2.0 Hz, 1H), 8.05 (d, *J* = 2.0 Hz, 1H), 8.64 (dd, *J* = 1.0, 6.8 Hz, 1H).

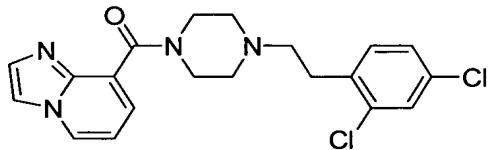
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Example 1.19: Preparation of (4-(2-Fluorophenethyl)piperazin-1-yl)(imidazo[1,2-*a*]pyridin-8-yl)methanone (Compound 18).



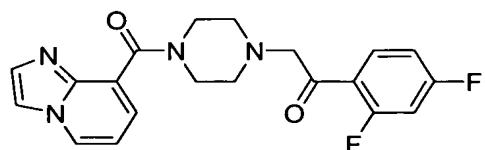
The title compound was prepared in a manner similar to that described in Example 1.13, step C, using imidazo[1,2-a]pyridin-8-yl(piperazin-1-yl)methanone hydrochloride (65 mg, 244 µmol) and 1-(2-bromoethyl)-2-fluorobenzene (59 mg, 292 µmol) as starting materials, to afford 5 the TFA salt as a solid (38 mg). Exact mass calculated for C₂₀H₂₁FN₄O: 352.2. Found: LCMS *m/z* = 353.4 (M + H)⁺. ¹H NMR (400 MHz, Acetonitrile-*d*₃) δ 3.09-3.16 (m, 2H) 3.24-3.34 (m, 2H), 3.35-3.55 (m, 8H), 7.07-7.19 (m, 2H), 7.27-7.35 (m, 2H), 7.41-7.47 (m, 1H), 7.83-7.87 (m, 1H), 7.91-7.94 (m, 1H), 8.05-8.08 (m, 1H), 8.65 (d, *J* = 6.8 Hz, 1H).

10 **Example 1.20: Preparation of (4-(2,4-Dichlorophenethyl)piperazin-1-yl)(imidazo[1,2-a]pyridin-8-yl)methanone (Compound 19).**



The title compound was prepared in a manner similar to that described in Example 1.13, step C, using imidazo[1,2-a]pyridin-8-yl(piperazin-1-yl)methanone hydrochloride (65 mg, 244 µmol) and 1-(2-bromoethyl)-2,4-dichlorobenzene (74 mg, 292 µmol) as starting materials, to afford 15 the TFA salt as a solid (41.0 mg). Exact mass calculated for C₂₀H₂₀Cl₂N₄O: 402.1. Found: LCMS *m/z* (%) = 403.4 ((M + H)⁺, ³⁵Cl, ³⁵Cl, 100%), 405.2 ((M + H)⁺, ³⁵Cl, ³⁷Cl, 64%). ¹H NMR (400 MHz, Acetonitrile-*d*₃) δ 3.16-3.29 (m, 4H) 3.30-3.90 (m, 8H), 7.30-7.36 (m, 2H), 7.38-7.45 (m, 1H), 7.50 (s, 1H), 7.80-7.86 (m, 1H), 7.92 (s, 1H), 8.05 (d, *J* = 2.0 Hz, 1H), 8.64 (d, *J* = 7.1 Hz, 1H).

20 **Example 1.21: Preparation of 1-(2,4-Difluorophenyl)-2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)ethanone (Compound 20).**

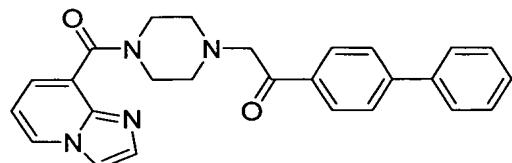


25 The title compound was prepared in a manner similar to that described in Example 1.13, step C, using imidazo[1,2-a]pyridin-8-yl(piperazin-1-yl)methanone hydrochloride (100 mg, 375 µmol) and 2-bromo-1-(2,4-difluorophenyl)ethanone (106 mg, 450 µmol) as starting materials, to afford the TFA salt of the title compound as a solid (96.2 mg). Exact mass calculated for

$C_{20}H_{18}F_2N_4O_2$: 384.1. Found: LCMS m/z = 385.4 ($M + H$)⁺. 1H NMR (400 MHz, Acetonitrile- d_3) δ 3.30-4.30 (m, 8H), 4.65 (d, J = 2.2 Hz, 2H), 7.11-7.19 (m, 2H), 7.45 (t, J = 7.1 Hz, 1H), 7.87 (dd, J = 1.0, 7.2 Hz, 1H), 7.92 (d, J = 2.0 Hz, 1H), 8.01-8.04 (m, 1H), 8.05 (d, J = 2.0 Hz, 1H), 8.66 (dd, J = 1.0, 7.2 Hz, 1H).

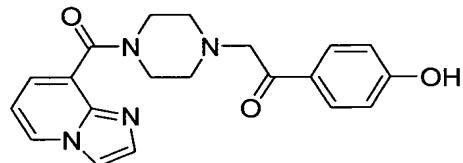
5

Example 1.22: Preparation of 1-(Biphenyl-4-yl)-2-(4-(imidazo[1,2-*a*]pyridine-8-carbonyl)piperazin-1-yl)ethanone (Compound 25).



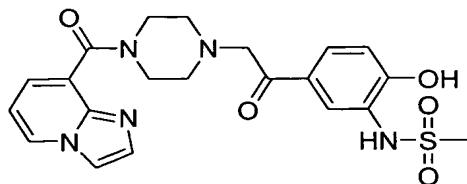
1-(Biphenyl-4-yl)-2-bromoethanone (57 mg, 208 μ mol) was added to a solution of 10 imidazo[1,2-*a*]pyridin-8-yl(piperazin-1-yl)methanone (40 mg, 174 μ mol) and potassium carbonate (72 mg, 521 μ mol) in DMSO (1.0 mL). The mixture was stirred at 28 °C for 1 hour. The residue was purified by preparative LCMS to afford the TFA salt of the title compound (23 mg) as a solid. Exact mass calculated for $C_{26}H_{24}N_4O_2$: 424.2; found: LCMS m/z = 425.0 ($M+H$)⁺. 1H NMR (400 MHz, Acetonitrile- d_4) δ 3.34-3.50 (m, 2H), 3.50-3.70 (m, 2H), 3.70-15 3.94 (m, 2H), 3.94-4.23 (m, 2H), 4.77 (s, 2H), 7.39 (t, J = 7.07 Hz, 1H), 7.43-7.48 (m, 1H), 7.49-7.54 (m, 2H), 7.73 (d, J = 8.08 Hz, 2H), 7.78-7.85 (m, 3H), 7.90 (d, J = 2.02 Hz, 1H), 8.01-8.05 (m, 3H), 8.62 (d, J = 7.07 Hz, 1H).

20 **Example 1.23: Preparation of 1-(4-Hydroxyphenyl)-2-(4-(imidazo[1,2-*a*]pyridine-8-carbonyl)piperazin-1-yl)ethanone (Compound 40).**



The title compound was prepared in a manner similar to that described in Example 1.22, using 2-bromo-1-(4-hydroxyphenyl)ethanone (45 mg, 208 μ mol), and imidazo[1,2-*a*]pyridin-8-yl(piperazin-1-yl)methanone (40 mg, 174 μ mol) as starting materials, to afford the TFA salt (21 mg) as a solid. Exact mass calculated for $C_{20}H_{20}N_4O_3$: 364.2; found: LCMS m/z = 365.1 ($M+H$)⁺. 1H NMR (400 MHz, Acetonitrile- d_4) δ 2.81-3.30 (m, 4H), 3.47 (bs, 2H), 3.94 (bs, 2H), 4.77 (s, 2H), 6.94 (d, J = 8.59 Hz, 2H), 7.45-7.50 (m, 1H), 7.85 (d, J = 8.59 Hz, 2H), 7.90-7.95 (m, 2H), 8.10-8.14 (m, 1H), 8.69-8.74 (m, 1H).

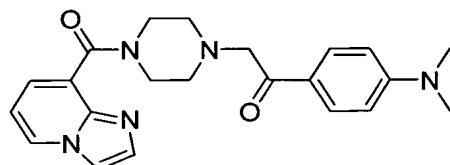
30 **Example 1.24: Preparation of *N*-(2-Hydroxy-5-(2-(4-(imidazo[1,2-*a*]pyridine-8-carbonyl)piperazin-1-yl)acetyl)phenyl)methanesulfonamide (Compound 23).**



The title compound was prepared in a manner similar to that described in Example 1.22, using *N*-(5-(2-bromoacetyl)-2-hydroxyphenyl)methanesulfonamide (64 mg, 208 μ mol), and imidazo[1,2-*a*]pyridin-8-yl(piperazin-1-yl)methanone (40 mg, 174 μ mol) as starting materials, 5 to afford the TFA salt (18 mg) as a solid. Exact mass calculated for $C_{21}H_{23}N_5O_5S$: 457.1; found: LCMS *m/z* = 458.2 ($M+H$)⁺. ¹H NMR (400 MHz, D₂O) δ 2.90 (s, 3H), 3.80 (bs, 4H), 4.23 (bs, 4H), 5.19 (s, 2H), 7.31 (d, *J* = 8.59 Hz, 1H), 7.74 (t, *J* = 7.07 Hz, 1H), 8.03 (d, *J* = 8.59 Hz, 1H), 8.13 (s, 1H), 8.18 (s, 1H), 8.27 (d, *J* = 7.07 Hz, 1H), 8.39 (s, 1H), 9.02 (d, *J* = 7.07 Hz, 1H).

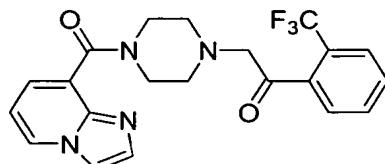
10

Example 1.25: Preparation of 1-(4-(Dimethylamino)phenyl)-2-(4-(imidazo[1,2-*a*]pyridine-8-carbonyl)piperazin-1-yl)ethanone (Compound 41).



The title compound was prepared in a manner similar to that described in Example 1.22, 15 using 2-bromo-1-(4-(dimethylamino)phenyl)ethanone (50 mg, 208 μ mol), and imidazo[1,2-*a*]pyridin-8-yl(piperazin-1-yl)methanone (40 mg, 174 μ mol) as starting materials, to afford the TFA salt (33 mg) as a solid. Exact mass calculated for $C_{22}H_{25}N_5O_2$: 391.2; found: LCMS *m/z* = 392.5 ($M+H$)⁺. ¹H NMR (400 MHz, Acetonitrile-*d*₄) δ 3.07 (s, 6H), 3.33-3.50 (m, 2H), 3.56-3.71 (m, 2H), 3.71-3.90 (m, 2H), 4.03-4.22 (m, 2H), 4.65 (s, 2H), 6.75 (d, *J* = 9.09 Hz, 2H), 20 7.39 (t, *J* = 7.07 Hz, 1H), 7.77-7.81 (m, 3H), 7.91 (d, *J* = 1.77 Hz, 1H), 8.04 (d, *J* = 1.77 Hz, 1H), 8.63 (d, *J* = 6.82 Hz, 1H).

Example 1.26: Preparation of 2-(4-(Imidazo[1,2-*a*]pyridine-8-carbonyl)piperazin-1-yl)-1-(2-(trifluoromethyl)phenyl)ethanone (Compound 38).



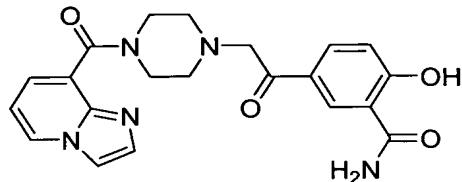
25

The title compound was prepared in a manner similar to that described in Example 1.22, using 2-bromo-1-(2-(trifluoromethyl)phenyl)ethanone (56 mg, 208 μ mol), and imidazo[1,2-*a*]pyridin-8-yl(piperazin-1-yl)methanone (40 mg, 174 μ mol) as starting materials, to afford the

TFA salt (5.7 mg) as a solid. Exact mass calculated for $C_{21}H_{19}F_3N_4O_2$: 416.2; found: LCMS m/z = 417.2 ($M+H$)⁺.

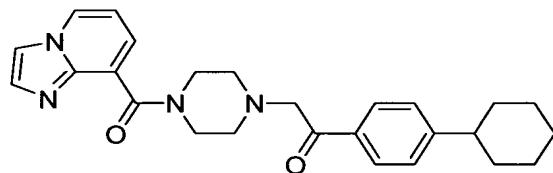
Example 1.27: Preparation of 2-Hydroxy-5-(2-(4-(imidazo[1,2-*a*]pyridine-8-

5 **carbonyl)piperazin-1-yl)acetyl)benzamide (Compound 37).**



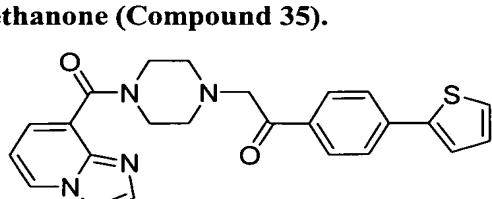
The title compound was prepared in a manner similar to that described in Example 1.22, using 5-(2-bromoacetyl)-2-hydroxybenzamide (54 mg, 208 μ mol), and imidazo[1,2-*a*]pyridin-8-yl(piperazin-1-yl)methanone (40 mg, 174 μ mol) as starting materials, to afford the TFA salt (25 mg) as a solid. Exact mass calculated for $C_{21}H_{21}N_5O_4$: 407.2; found: LCMS m/z = 408.2 ($M+H$)⁺. 1H NMR (400 MHz, Acetonitrile-*d*₄) δ 2.74-4.26 (m, 8H), 4.90 (s, 2H), 6.56 (bs, 1H), 7.05 (d, *J* = 8.84 Hz, 1H), 7.45 (t, *J* = 7.07 Hz, 1H), 7.85-7.89 (m, 2H), 7.98-8.10 (bs, 1H), 8.02 (d, *J* = 8.84 Hz, 1H), 8.07 (d, *J* = 1.77 Hz, 1H), 8.51 (s, 1H), 8.66 (d, *J* = 6.57 Hz, 1H).

15 **Example 1.28: Preparation of 1-(4-Cyclohexylphenyl)-2-(4-(imidazo[1,2-*a*]pyridine-8-carbonyl)piperazin-1-yl)ethanone (Compound 28).**



The title compound was prepared in a manner similar to that described in Example 1.22, using 2-bromo-1-(4-cyclohexylphenyl)ethanone (59 mg, 208 μ mol), and imidazo[1,2-*a*]pyridin-8-yl(piperazin-1-yl)methanone (40 mg, 174 μ mol) as starting materials, to afford the TFA salt (13 mg) as a solid. Exact mass calculated for $C_{26}H_{30}N_4O_2$: 430.2; found: LCMS m/z = 431.0 ($M+H$)⁺.

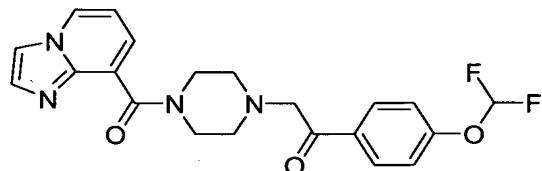
25 **Example 1.29: Preparation of 2-(4-(Imidazo[1,2-*a*]pyridine-8-carbonyl)piperazin-1-yl)-1-(4-(thiophen-2-yl)phenyl)ethanone (Compound 35).**



The title compound was prepared in a manner similar to that described in Example 1.22, using 2-bromo-1-(4-(thiophen-2-yl)phenyl)ethanone (59 mg, 208 μ mol), and imidazo[1,2-

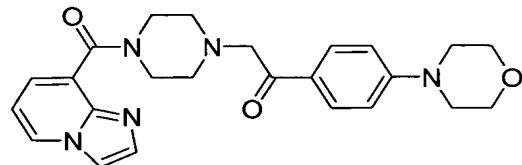
a]pyridin-8-yl(piperazin-1-yl)methanone (40 mg, 174 µmol) as starting materials, to afford the TFA salt (17 mg) as a solid. Exact mass calculated for C₂₄H₂₂N₄O₂S: 430.2; found: LCMS *m/z* = 431.1 (M+H)⁺.

5 **Example 1.30: Preparation of 1-(4-(Difluoromethoxy)phenyl)-2-(4-(imidazo[1,2-*a*]pyridine-8-carbonyl)piperazin-1-yl)ethanone (Compound 29).**



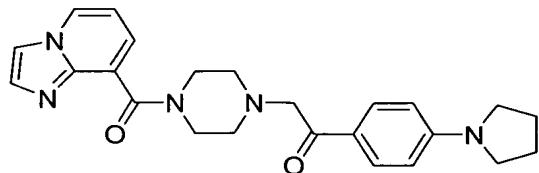
The title compound was prepared in a manner similar to that described in Example 1.22, using 2-bromo-1-(4-(difluoromethoxy)phenyl)ethanone (55 mg, 208 µmol), and imidazo[1,2-*a*]pyridin-8-yl(piperazin-1-yl)methanone (40 mg, 174 µmol) as starting materials, to afford the TFA salt (5 mg) as a solid. Exact mass calculated for C₂₁H₂₀F₂N₄O₃: 414.2; found: LCMS *m/z* = 414.9 (M+H)⁺.

10 **Example 1.31: Preparation of 2-(4-(Imidazo[1,2-*a*]pyridine-8-carbonyl)piperazin-1-yl)-1-(4-morpholinophenyl)ethanone (Compound 43).**



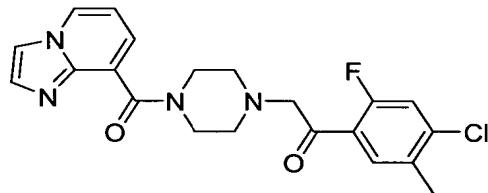
The title compound was prepared in a manner similar to that described in Example 1.22, using 2-bromo-1-(4-morpholinophenyl)ethanone (59 mg, 208 µmol), and imidazo[1,2-*a*]pyridin-8-yl(piperazin-1-yl)methanone (40 mg, 174 µmol) as starting materials, to afford the TFA salt (32 mg) as a solid. Exact mass calculated for C₂₄H₂₇N₅O₃: 433.2; found: LCMS *m/z* = 434.2 (M+H)⁺. ¹H NMR (400 MHz, Acetonitrile-*d*₄) δ 3.36 (bt, *J* = 4.80 Hz, 4H), 3.39–4.38 (m, 8H), 3.77 (bt, *J* = 4.80 Hz, 4H), 4.70 (s, 2H), 6.96 (d, *J* = 8.84 Hz, 2H), 7.44 (t, *J* = 7.07 Hz, 1H), 7.82 (d, *J* = 8.84 Hz, 2H), 7.85 (d, *J* = 7.33 Hz, 1H), 7.92 (d, *J* = 1.77 Hz, 1H), 8.06 (d, *J* = 1.77 Hz, 1H), 8.65 (d, *J* = 6.82 Hz, 1H).

15 **Example 1.32: Preparation of 2-(4-(Imidazo[1,2-*a*]pyridine-8-carbonyl)piperazin-1-yl)-1-(4-(pyrrolidin-1-yl)phenyl)ethanone (Compound 21).**



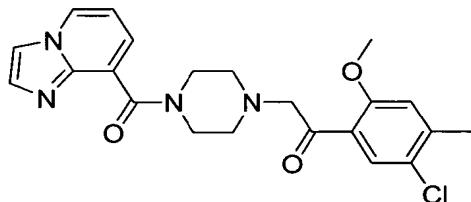
The title compound was prepared in a manner similar to that described in Example 1.22, using 2-bromo-1-(4-(pyrrolidin-1-yl)phenyl)ethanone (56 mg, 208 µmol), and imidazo[1,2-a]pyridin-8-yl(piperazin-1-yl)methanone (40 mg, 174 µmol) as starting materials, to afford the TFA salt (31 mg) as a solid. Exact mass calculated for C₂₄H₂₇N₅O₂: 417.2; found: LCMS *m/z* = 418.4 (M+H)⁺.

Example 1.33: Preparation of 1-(4-Chloro-2-fluoro-5-methylphenyl)-2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)ethanone (Compound 31).



The title compound was prepared in a manner similar to that described in Example 1.22, using 2-bromo-1-(4-chloro-2-fluoro-5-methylphenyl)ethanone (55 mg, 208 µmol), and imidazo[1,2-a]pyridin-8-yl(piperazin-1-yl)methanone (40 mg, 174 µmol) as starting materials, to afford the TFA salt (1.6 mg) as a solid. Exact mass calculated for C₂₁H₂₀ClFN₄O₂: 414.1; found: LCMS *m/z* (%) = 415.1 ((M+H)⁺ ³⁵Cl, 100%), 417.2 ((M+H)⁺ ³⁷Cl, 32%).

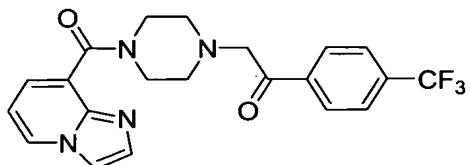
Example 1.34: Preparation of 1-(5-Chloro-2-methoxy-4-methylphenyl)-2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)ethanone (Compound 32).



The title compound was prepared in a manner similar to that described in Example 1.22, using 2-bromo-1-(5-chloro-2-methoxy-4-methylphenyl)ethanone (58 mg, 208 µmol), and imidazo[1,2-a]pyridin-8-yl(piperazin-1-yl)methanone (40 mg, 174 µmol) as starting materials, to afford the TFA salt (29 mg) as a solid. Exact mass calculated for C₂₂H₂₃ClN₄O₃: 426.1; found: LCMS *m/z* (%) = 427.1 ((M+H)⁺ ³⁵Cl, 100%), 429.1 ((M+H)⁺ ³⁷Cl, 32%). ¹H NMR (400

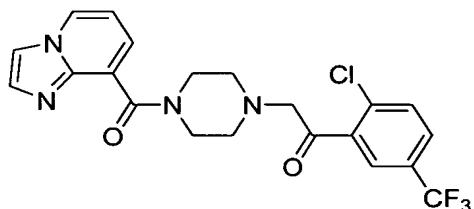
MHz, Acetonitrile-*d*₄) δ 2.43 (s, 3H), 3.28-4.46 (m, 8H), 3.96 (s, 3H), 4.62 (s, 2H), 7.14 (s, 1H), 7.42 (t, *J* = 7.07 Hz, 1H), 7.81-7.85 (m, 2H), 7.93 (s, 1H), 8.06 (s, 1H), 8.64 (d, *J* = 7.07 Hz, 1H).

5 **Example 1.35: Preparation of 2-(4-(Imidazo[1,2-*a*]pyridine-8-carbonyl)piperazin-1-yl)-1-(4-(trifluoromethyl)phenyl)ethanone (Compound 34).**



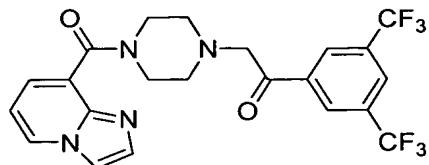
The title compound was prepared in a manner similar to that described in Example 1.22,
10 using 2-bromo-1-(4-(trifluoromethyl)phenyl)ethanone (42 mg, 156 μmol), and imidazo[1,2-*a*]pyridin-8-yl(piperazin-1-yl)methanone (30 mg, 130 μmol) as starting materials, to afford the TFA salt (48 mg) as a solid. Exact mass calculated for C₂₁H₁₉F₃N₄O₂: 416.2; found: LCMS *m/z* = 417.5 (M+H)⁺.

15 **Example 1.36: Preparation of 1-(2-Chloro-5-(trifluoromethyl)phenyl)-2-(4-(imidazo[1,2-*a*]pyridine-8-carbonyl)piperazin-1-yl)ethanone (Compound 24).**



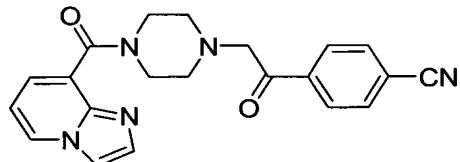
The title compound was prepared in a manner similar to that described in Example 1.22,
20 using 2-bromo-1-(2-chloro-5-(trifluoromethyl)phenyl)ethanone (47 mg, 156 μmol), and imidazo[1,2-*a*]pyridin-8-yl(piperazin-1-yl)methanone (30 mg, 130 μmol) as starting materials, to afford the TFA salt (54 mg) as a solid. Exact mass calculated for C₂₁H₁₈ClF₃N₄O₂: 450.1; found: LCMS *m/z* (%) = 451.3 ((M+H)⁺ ³⁵Cl, 100%), 453.3 ((M+H)⁺ ³⁷Cl, 32%). ¹H NMR (400 MHz, Acetonitrile-*d*₄) δ 3.50 (bs, 4H), 3.95 (bs, 4H), 4.70 (s, 2H), 7.46 (t, *J* = 7.07 Hz, 1H), 7.76 (d, *J* = 8.59 Hz, 1H), 7.86-7.92 (m, 3H), 8.07 (d, *J* = 6.57 Hz, 2H), 8.66 (d, *J* = 7.07 Hz, 1H).

Example 1.37: Preparation of 1-(3,5-Bis(trifluoromethyl)phenyl)-2-(4-(imidazo[1,2-*a*]pyridine-8-carbonyl)piperazin-1-yl)ethanone (Compound 33).



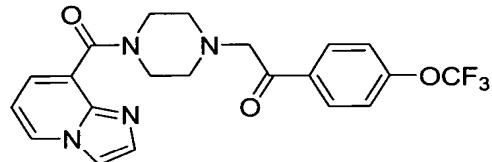
The title compound was prepared in a manner similar to that described in Example 1.22, using 1-(3,5-bis(trifluoromethyl)phenyl)-2-bromoethanone (52 mg, 156 µmol), and imidazo[1,2-a]pyridin-8-yl(piperazin-1-yl)methanone (30 mg, 130 µmol) as starting materials, to afford the TFA salt (30 mg) as a solid. Exact mass calculated for $C_{22}H_{18}F_6N_4O_2$: 484.1; found: LCMS m/z = 485.4 ($M+H$)⁺. 1H NMR (400 MHz, Acetonitrile-*d*₄) δ 3.52 (bs, 4H), 3.98 (bs, 4H), 4.87 (s, 2H), 7.47 (t, J = 7.07 Hz, 1H), 7.89-7.92 (m, 2H), 8.08 (d, J = 1.52 Hz, 1H), 8.33 (s, 1H), 8.46 (s, 2H), 8.67 (d, J = 7.07 Hz, 1H).

10 **Example 1.38: Preparation of 4-(2-(4-(Imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)acetyl)benzonitrile (Compound 39).**



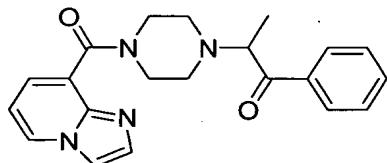
The title compound was prepared in a manner similar to that described in Example 1.22, using 4-(2-bromoacetyl)benzonitrile (35 mg, 156 µmol), and imidazo[1,2-a]pyridin-8-yl(piperazin-1-yl)methanone (30 mg, 130 µmol) as starting materials, to afford the TFA salt (23 mg) as a solid. Exact mass calculated for $C_{21}H_{19}N_5O_2$: 373.2; found: LCMS m/z = 374.3 ($M+H$)⁺.

20 **Example 1.39: Preparation of 2-(4-(Imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)-1-(4-(trifluoromethoxy)phenyl)ethanone (Compound 22).**



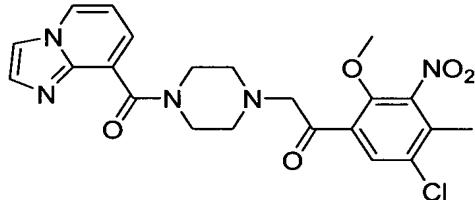
The title compound was prepared in a manner similar to that described in Example 1.22, using 2-bromo-1-(4-(trifluoromethoxy)phenyl)ethanone (44 mg, 156 µmol), and imidazo[1,2-a]pyridin-8-yl(piperazin-1-yl)methanone (30 mg, 130 µmol) as starting materials, to afford the TFA salt (22 mg) as a solid. Exact mass calculated for $C_{21}H_{19}F_3N_4O_3$: 432.1; found: LCMS m/z = 433.2 ($M+H$)⁺.

Example 1.40: Preparation of 2-(4-(Imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)-1-phenylpropan-1-one(Compound 30).



The title compound was prepared in a manner similar to that described in Example 1.22,
 5 using 2-bromo-1-phenylpropan-1-one (33 mg, 156 μ mol), and imidazo[1,2-a]pyridin-8-yl(piperazin-1-yl)methanone (30 mg, 130 μ mol) as starting materials, to afford the TFA salt (29 mg) as a solid. Exact mass calculated for $C_{21}H_{22}N_4O_2$: 362.2; found: LCMS m/z = 363.5 ($M+H$)⁺.

10 **Example 1.41: Preparation of 1-(5-Chloro-2-methoxy-4-methyl-3-nitrophenyl)-2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)ethanone (Compound 42).**



The title compound was prepared in a manner similar to that described in Example 1.22,
 using 2-bromo-1-(5-chloro-2-methoxy-4-methyl-3-nitrophenyl)ethanone (50 mg, 156 μ mol),
 15 and imidazo[1,2-a]pyridin-8-yl(piperazin-1-yl)methanone (30 mg, 130 μ mol) as starting
 materials, to afford the TFA salt (14 mg) as a solid. Exact mass calculated for $C_{22}H_{22}ClN_5O_5$:
 471.1; found: LCMS m/z (%) = 472.5 (($M+H$)⁺ ^{35}Cl , 100%), 474.6 (($M+H$)⁺ ^{37}Cl , 32%).

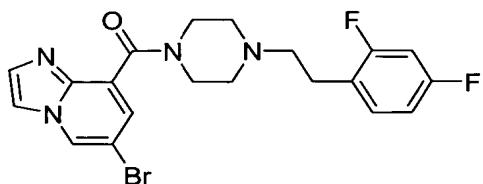
20 **Example 1.42: Preparation of (6-Bromoimidazo[1,2-a]pyridin-8-yl)(4-(2,4-difluorophenethyl)piperazin-1-yl)methanone (Compound 44).**

Step A: Preparation of 6-Bromoimidazo[1,2-a]pyridine-8-carboxylic acid.



The title compound was prepared in a manner similar to that described in Example 1.3,
 Step A, using 5-bromo-2-aminonicotinic acid (0.109 g) and chloroacetaldehyde (7.75 M, 0.077
 25 mL, 0.600 mmol) as starting materials (heated 30 minutes at 150 °C under microwave) to afford
 a grey solid (0.067 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.98 (d, *J*=1.52 Hz, 1 H), 8.22 (d,
J=1.77 Hz, 1 H), 8.25 (s, 1 H), 9.37 (d, *J*=1.52 Hz, 1 H).

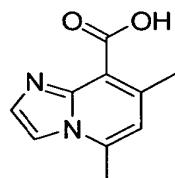
Step B: Preparation of (6-Bromoimidazo[1,2-*a*]pyridin-8-yl)(4-(2,4-difluorophenethyl)piperazin-1-yl)methanone (Compound 44).



The title compound was prepared in a manner similar to that described in Example 1.3,
 5 Step E, using 6-bromoimidazo[1,2-*a*]pyridine-8-carboxylic acid (36.2 mg, 0.150 mmol), 1-(2,4-difluorophenethyl)piperazine dihydrochloride (29.9 mg, 0.100 mmol) as starting materials to afford a white solid (24.3 mg). Exact mass for $C_{20}H_{19}BrF_2N_4O$: 448.1; found: LCMS *m/z* = 449.1($(M+H)^+$, 100%), 451.1 ($(M+H)^+$, 80). 1H NMR (400 MHz, $CDCl_3$) δ 2.50 (br s, 2H), 2.57-2.64 (m, 2H), 2.67 (br s, 2H), 2.75-2.84 (m, 2H), 3.30-3.39 (m, 2H), 3.85-3.96 (m, J = 4.29 Hz, 2H), 6.73-6.83 (m, 2H), 7.11-7.20 (m, 1H), 7.33 (d, J = 1.77 Hz, 1H), 7.61 (d, J = 1.01 Hz, 1H), 7.68 (d, J = 1.01 Hz, 1H), 8.33 (d, J = 1.77 Hz, 1H).

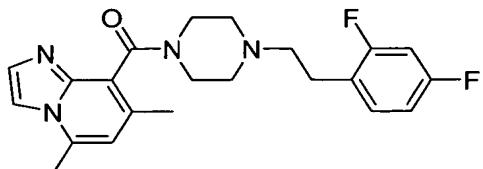
Example 1.43: Preparation of (4-(2,4-Difluorophenethyl)piperazin-1-yl)(5,7-dimethylimidazo[1,2-*a*]pyridin-8-yl)methanone (Compound 27).

Step A: Preparation of 5,7-Dimethylimidazo[1,2-*a*]pyridine-8-carboxylic Acid.



To a mixture of 2-amino-4,6-dimethylnicotinic acid hydrochloride salt (0.101 g, 0.500 mmol) in water (2.5 mL) was added NaOH (1.0 M, 0.5 mL) and chloroacetaldehyde (7.75 M, 0.077 mL, 0.600 mmol). The resulting slurry was heated to 150 °C under microwave irradiation 20 for 30 min. The crude mixture was purified *via* preparative HPLC/MS. The resultant TFA salt obtained was taken up in ACN and treated with 4.0 M HCl in dioxane (1.25 mL) and reduced under reduced pressure to afford the title compound (0.108 g) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 2.75 (s, 3H) 2.78 (s, 3H), 7.46 (s, 1H), 8.17 (d, J = 2.27 Hz, 1H), 8.39 (d, J = 2.27 Hz, 1H).

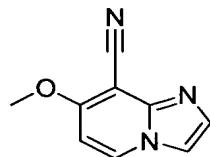
Step B: Preparation of (4-(2,4-Difluorophenethyl)piperazin-1-yl)(5,7-dimethylimidazo[1,2-a]pyridin-8-yl)methanone (Compound 27).



The title compound was prepared in a manner similar to that described in Example 1.3, Step E, using 5,7-dimethylimidazo[1,2-*a*]pyridine-8-carboxylic acid (34.0 mg, 0.150 mmol), 1-(2,4-difluorophenethyl)piperazine dihydrochloride (29.9 mg, 0.100 mmol) as starting materials to afford a white solid (31.6 mg). Exact mass for C₂₂H₂₄F₂N₄O: 398.2; found: LCMS *m/z* = 5 399.1 (M+H)⁺. ¹H NMR (400 MHz, CDCl₃) δ 2.35 (s, 3H) 2.56 (s, 3H), 2.57-2.63 (m, 4H), 2.74-2.80 (m, 4H), 3.19-3.27 (m, 1H), 3.30-3.37 (m, 1H), 3.84-3.93 (m, 1H), 3.96-4.07 (m, 1H), 6.51 (s, 1H), 6.72-6.84 (m, 2H), 7.11-7.19 (m, 1H), 7.42 (s, 1H), 7.65 (s, 1H).

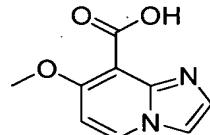
Example 1.44: Preparation of (4-(2,4-Difluorophenethyl)piperazin-1-yl)(7-methoxyimidazo[1,2-*a*]pyridin-8-yl)methanone (Compound 36).

Step A: Preparation of 7-Methoxyimidazo[1,2-*a*]pyridine-8-carbonitrile.



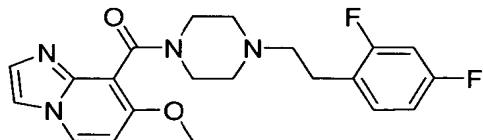
To a solution of 2-amino-4-methoxynicotinonitrile (1.491 g, 10.0 mmol) in water (20.00 ml) was added 2-chloroacetaldehyde (1.548 mL, 12.00 mmol) and the reaction was heated to 80 15 °C in an oil bath overnight. The reaction was cooled to room temperature, NaOH (10.00 ml, 10.00 mmol) was added and the resulting precipitate was filtered off and washed with water to afford the title compound (1.621 g) as a tan solid. ¹H NMR (400 MHz, DMSO-d₆) δ 4.05 (s, 3H), 7.13 (d, *J* = 7.70 Hz, 1H), 7.52 (d, *J* = 1.35 Hz, 1H), 7.92 (d, *J* = 1.35 Hz, 1H), 8.84 (d, *J* = 7.70 Hz, 1H).

Step B: Preparation of 7-Methoxyimidazo[1,2-*a*]pyridine-8-carboxylic Acid.



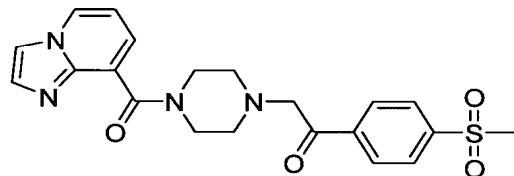
To a mixture of 7-methoxyimidazo[1,2-*a*]pyridine-8-carbonitrile (0.173 g, 1.00 mmol) and water (1.000 ml) was added 3.75 M NaOH (0.400 ml, 1.500 mmol), the resulting mixture was heated to 160 °C under microwave irradiation for 30 min. The reaction was treated with 1.0 25 M HCl (1.000 ml, 1.000 mmol), the resulting precipitate was filtered off and washed with water. The mother liquor was reduced under reduced pressure to afford a crude mixture (76.0%) of the title compound (0.117 g) as a tan solid. Exact mass for C₉H₈N₂O₃: 192.1; found: LCMS *m/z* = 193.2 (M+H)⁺.

Step C: Preparation of (4-(2,4-difluorophenethyl)piperazin-1-yl)(7-methoxyimidazo[1,2-*a*]pyridin-8-yl)methanone (Compound 36).



The title compound was prepared in a manner similar to that described in Example 1.3, Step E, using 7-methoxyimidazo[1,2-a]pyridine-8-carboxylic acid (28.8 mg, 0.150 mmol), 1-(2,4-difluorophenethyl)piperazine dihydrochloride (29.9 mg, 0.100 mmol) as starting materials 5 to afford a white solid (13.9 mg). Exact mass for C₂₁H₂₂F₂N₄O₂: 400.2; found: LCMS *m/z* = 401.3 (M+H)⁺. ¹H NMR (400 MHz, CDCl₃) δ 2.55-2.65 (m, 6H), 2.77-2.81 (m, 2H), 3.33-3.39 (m, 2H), 3.93 (s, 3H), 3.91-3.97 (m, 2H), 6.70 (d, *J* = 7.54 Hz, 1H), 6.74-6.82 (m, 2H), 7.13-7.19 (m, 1H), 7.48 (d, *J* = 1.25 Hz, 1H), 7.56 (d, *J* = 1.25 Hz, 1H), 8.92 (d, *J* = 7.54 Hz, 1H).

10 **Example 1.45: Preparation of 2-(4-(Imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)-1-(4-(methylsulfonyl)phenyl)ethanone (Compound 26).**



The title compound was prepared in a manner similar to that described in Example 1.22, using 2-bromo-1-(4-(methylsulfonyl)phenyl)ethanone (43 mg, 156 μmol), and imidazo[1,2-a]pyridin-8-yl(piperazin-1-yl)methanone (30 mg, 130 μmol) as starting materials, to afford the TFA salt (13 mg) as a solid. Exact mass calculated for C₂₁H₂₂N₄O₄S: 426.1; found: LCMS *m/z* (%) = 427.3 (M+H)⁺.

Example 2: Receptor Expression.

20 **A. pCMV**

Although a variety of expression vectors are available to those in the art, it is preferred that the vector utilized be pCMV. This vector was deposited with the American Type Culture Collection (ATCC) on October 13, 1998 (10801 University Blvd., Manassas, VA 20110-2209 USA) under the provisions of the Budapest Treaty for the International Recognition of the 25 Deposit of Microorganisms for the Purpose of Patent Procedure. The DNA was tested by the ATCC and determined to be viable. The ATCC has assigned the following deposit number to pCMV: ATCC #203351.

B. Transfection Procedure

For the IP accumulation assay (Example 3), HEK293 cells were transfected while for 30 the DOI binding assay (Example 3) COS7 cells were transfected. Several protocols well known

in the art can be used to transfect cells. The following protocol is representative of the transfection procedures used herein for COS7 or 293 cells.

On day one, COS-7 cells were plated onto 24 well plates, usually 1×10^5 cells/well or 2×10^5 cells/well, respectively. On day two, the cells were transfected by first mixing 0.25 μ g cDNA in 50 μ L serum-free DMEM/well and then 2 μ L lipofectamine in 50 μ L serum-free DMEM/well. The solutions (“transfection media”) were gently mixed and incubated for 15-30 min at room temperature. The cells were washed with 0.5 mL PBS and then 400 μ L of serum free medium was mixed with the transfection media and added to the cells. The cells were then incubated for 3-4 hours at 37 °C/5% CO₂. Then the transfection medium was removed and replaced with 1 mL/well of regular growth medium.

For 293 cells, on day one, 13×10^6 293 cells per 150 mm plate were plated out. On day two, 2 mL of serum OptimemI (Invitrogen Corporation) was added per plate followed by addition of 60 μ L of lipofectamine and 16 μ g of cDNA. Note that lipofectamine must be added to the OptimemI and mixed well before addition of cDNA. While complexes between lipofectamine and the cDNA are forming, the medium was carefully aspirated and cells were gently rinsed with 5 mL of OptimemI medium followed by careful aspiration. Then 12 mL of OptimemI was added to each plate and 2 mL of transfection solution was added followed by a 5 h incubation at 37 °C in a 5% CO₂ incubator. Plates were then carefully aspirated and 25 mL of Complete Media were added to each plate and cells were then incubated until used.

20

Example 3: Binding Assays.

Compounds of the invention were tested for their ability to bind to a 5-HT_{2A} serotonin receptor clone membrane preparation using a radioligand binding assay. Briefly, COS cells were transiently transfected with a pCMV expression vector containing a human 5-HT_{2A} receptor (for the sequence of the receptor see U.S. Patent No. 6,541,209, SEQ ID NO:24).

A. Preparation of Crude Membrane Preparations for Radioligand Binding Assays.

COS7 cells transfected with recombinant human 5-HT_{2A} serotonin receptors were cultured for 48 h post transfection, collected, washed with ice-cold phosphate buffered saline, pH 7.4 (PBS) and then centrifuged at 48,000 g for 20 min at 4 °C. The cell pellet was then resuspended in wash buffer containing 20 mM HEPES, pH 7.4 and 0.1 mM EDTA, homogenized on ice using a Brinkman polytron and recentrifuged at 48,000 g for 20 min at 4 °C. The resultant pellet was then resuspended in 20 mM HEPES, pH 7.4, homogenized on ice and centrifuged (48,000 g for 20 min at 4 °C). Crude membrane pellets were stored at -80 °C until used for radioligand binding assays.

B. [¹²⁵I]DOI Radioligand Binding Assay.

Radioligand binding assays for human 5-HT_{2A} serotonin receptor were conducted using the 5-HT₂ agonist [¹²⁵I]DOI as radioligand. To define nonspecific binding, 10 µM DOI was used for all assays. For competitive binding studies, 0.5 nM [¹²⁵I]DOI was used and compounds were assayed over a range of 0.01 nM to 10 µM. Assays were conducted in a total volume of 5 200 µl in 96-well Perkin Elmer GF/C filter plates in assay buffer (50 mM Tris-HCl, pH 7.4, 0.5 mM EDTA, 5 mM MgCl₂ and 10 µM pargyline). Assay incubations were performed for 60 min at room temperature and were terminated by rapid filtration under reduced pressure of the reaction mixture over Whatman GF/C glass fiber filters presoaked in 0.5% PEI using a Brandell cell harvester. Filters were then washed several times with ice-cold wash buffer (50 mM Tris-10 HCl, pH 7.4). Plates were then dried at room temperature and counted in a Wallac MicroBeta scintillation counter. Certain compounds of the present invention and their corresponding activity values are shown in TABLE B.

TABLE B

Compound No.	IC ₅₀ DOI Binding Assay (nM)
9	46
10	10
17	4

15 Certain other compounds of the invention had activity values ranging from about 10 µM to about 1 nM in this assay.

Example 4: In vitro Human Platelet Aggregation Assays.

Compounds of the invention were tested for their ability to aggregate human platelets. 20 Aggregation assays were performed using a Chrono-Log Optical aggregometer model 410. Human blood (~100 mL) was collected from human donors into glass Vacutainers containing 3.8% sodium citrate (light blue tops) at room temperature. Platelet rich plasma (PRP) was isolated *via* centrifugation at 100 g for 15 min at room temperature. After removal of the aqueous PRP layer, the platelet poor plasma (PPP) was prepared *via* high speed centrifugation at 25 2400 g for 20 min. Platelets were counted and their concentration was set to 250,000 cells/µL by dilution with PPP. Aggregation assays were conducted according to the manufacturer's specifications. Briefly, a suspension of 450 µL PRP was stirred in a glass cuvette (1200 rpm) and, after baseline was established, 1 µM ADP followed by either saline or 1 µM 5-HT and compound of interest (at desired concentrations) were added and the aggregation response recorded. The concentration of ADP used causes approximately 10-20% of maximal aggregation. The 5-HT concentration corresponded to the concentration which produced maximal potentiation. Percent inhibition of aggregation was calculated from the maximum decrease in optical density of the controls and of the samples containing inhibitors. Only the 30

synergistic effect was assessed. Certain compounds of the invention had activity values ranging from about 80 μ M to about 15 nM in this assay. Other compounds of the invention had activity values ranging from about 8 μ M to about 50 nM in this assay.

5 **Example 5: Inositol Phosphate (IP) Accumulation Assays.**

A. **5-HT_{2A} Receptor**

Compounds of the invention can be tested for their ability to activate a 5-HT_{2A} receptor clone using an IP accumulation assay. Briefly, HEK293 cells are transiently transfected with a pCMV expression vector containing a human 5-HT_{2A} receptor (for the sequence of the receptor see U.S. Patent No. 6,541,209, SEQ ID NO:24). An IP accumulation assay can be performed as described in part C below.

B. **Constitutively Active 5-HT_{2A} Receptor**

Compounds of the invention can be tested for their ability to inhibit a constitutively active 5-HT_{2A} receptor clone using an IP accumulation assay. Briefly, 293 cells are transiently transfected with a pCMV expression vector containing a constitutively active human 5-HT_{2A} receptor (for the sequence of the receptor see U.S. Patent No. 6,541,209, SEQ ID NO:30). The constitutively active human 5-HT_{2A} receptor contains the human 5-HT_{2A} receptor described in part A except that intracellular loop 3 (IC3) and the cytoplasmic tail are replaced by the corresponding human INI 5-HT_{2C} cDNA. An IP accumulation assay can be performed as described in part C below.

C. **IP Accumulation Assay Protocol**

On the day after transfections, medium is removed and the cells are washed with 5 mL PBS followed by careful aspiration. Cells are then trypsinized with 2 mL of 0.05% trypsin for 20-30 s followed by addition of 10 mL of warmed medium, gently triturated to dissociate cells and an additional 13 mL of warmed medium is gently added. Cells are then counted and 55,000 cells are added to 96-well sterile poly-D-lysine treated plates. Cells are allowed to attach over a six hour incubation at 37 °C in a 5% CO₂ incubator. Medium is then carefully aspirated and 100 μ L of warm inositol-free medium plus 0.5 μ Ci ³H-inositol is added to each well and the plates are incubated for 18-20 h at 37 °C in a 5% CO₂ incubator.

On the next day, the medium is carefully aspirated and then 0.1 mL of assay medium is added containing inositol-free/serum free medium, 10 μ M pargyline, 10 mM lithium chloride and test compound at indicated concentrations. The plates are incubated for three hours at 37 °C and then the wells are carefully aspirated. Then 200 μ L of ice-cold 0.1 M formic acid is added to each well. Plates are then frozen at -80 °C until further processing. Frozen plates are thawed over the course of one hour and the contents of the wells (approximately 220 μ L) are placed over 400 μ L of washed ion-exchange resin (AG 1-X8) contained in a Multi-Screen Filtration plate and incubated for 10 min followed by filtration under reduced pressure. The resin is

washed nine times with 200 μ L of water and then tritiated inositol phosphates (IP, IP2 and IP3) are eluted into a collecting plate by the addition of 200 μ L of 1 M ammonium formate followed by an additional 10 min incubation. The eluent is then transferred to 20 mL scintillation vials, 8 mL of SuperMix or Hi-Safe scintillation cocktail is added and the vials are counted for 0.5-1
5 min in a Wallac 1414 scintillation counter.

Example 6: Efficacy of Compounds of the Invention in the Attenuation of DOI-induced Hypolocomotion in Rats.

In this example, compounds of the invention were tested for inverse agonist activity by
10 determining whether these compounds could attenuate DOI-induced hypolocomotion in rats in a novel environment. DOI is a potent 5-HT_{2A/2C} receptor agonist that crosses the blood-brain barrier. The standard protocol used is described briefly below.

Animals:

Male Sprague-Dawley rats weighing between 200-350 g were used for all tests. Rats
15 were housed three to four per cage.

Compounds:

(R)-DOI HCl ($C_{11}H_{16}INO_2.HCl$) was obtained from Sigma-Aldrich and was dissolved in 0.9% saline. Compounds of the invention were synthesized at Arena Pharmaceuticals Inc., San Diego, CA and were dissolved in 100% PEG400. DOI was injected s.c. in a volume of 1
20 mL/kg, while compounds of the invention were administered p.o. in a volume of 1 mL/kg.

Procedure:

The “Motor Monitor” (Hamilton-Kinder, Poway, CA) was used for all activity measurement. This apparatus recorded rears using infrared photobeams.

Locomotor activity testing was conducted during the light cycle between 9:00 a.m. and
25 4:00 p.m. Animals were allowed 30 min acclimation to the testing room before testing began.

In determining the effects of compounds of the invention on DOI-induced hypoactivity, animals were first injected with vehicle or the compound of the invention (1-10 mg/kg) in their home cages. Twenty five minutes later, saline or DOI (1 mg/kg salt) was injected. Ten minutes after DOI administration, animals were placed into the activity apparatus and rearing activity
30 was measured for 10 min.

Statistics and Results:

Results (total rears over 10 min) were analyzed by t-test. P < 0.05 was considered significant. As shown in **Figure 6**, compound **18** attenuated DOI-induced hypolocomotion in rats. In addition, as shown in **Figure 7**, compound **19** also attenuated DOI-induced
35 hypolocomotion in rats.

Example 7: Serotonin 5-HT_{2A} Receptor Occupancy Studies in Monkey.

In this example, the 5-HT_{2A} receptor occupancy of a compound of the invention can be measured. The study can be carried out in rhesus monkeys using PET and ¹⁸F-altanserin.

Radioligand:

The PET radioligand used for the occupancy studies is ¹⁸F-altanserin. Radiosynthesis of ¹⁸F-altanserin is achieved in high specific activities and is suitable for radiolabeling 5-HT_{2A} receptors *in vivo* (see Staley *et al.*, *Nucl. Med. Biol.*, 28:271-279 (2001) and references cited therein). Quality control issues (chemical and radiochemical purity, specific activity, stability, etc.) and appropriate binding of the radioligand are verified in rat brain slices prior to use in PET experiments.

10 Drug Doses and Formulations:

Briefly, the radiopharmaceutical is dissolved in sterile 0.9% saline, pH approx 6-7. The compounds of the invention are dissolved in a mixture of 60% PEG 400 and 40% sterile saline on the same day of the PET experiment.

Serotonin 5-HT_{2A} occupancy studies in humans have been reported for M100,907 (Grunder *et al.*, *Neuropsychopharmacology*, 17:175-185 (1997) and Talvik-Lofti *et al.*, *Psychopharmacology*, 148:400-403 (2000)). High occupancies of the 5-HT_{2A} receptors have been reported for various oral doses (doses studied ranged from 6 to 20 mg). For example, an occupancy of > 90% was reported for a dose of 20 mg (Talvik-Lofti *et al.*, *supra*), which translates to approx. 0.28 mg/kg. It may therefore be anticipated that an i.v. dose of 0.1 to 0.2 mg/kg of M100,907 is likely to provide high receptor occupancy. A 0.5 mg/kg dose of a Compound of the invention can be used in these studies.

PET Experiments:

The monkey is anesthetized by using ketamine (10 mg/kg) and is maintained using 0.7 to 1.25% isoflurane. Typically, the monkey has two i.v. lines, one on each arm. One i.v. line is used to administer the radioligand, while the other line is used to draw blood samples for pharmacokinetic data of the radioligand as well as the unlabeled drugs. Generally, rapid blood samples are taken as the radioligand is administered which then taper out by the end of the scan. A volume of approximately 1 mL of blood is taken per time point, which is spun down and a portion of the plasma is counted for radioactivity in the blood.

An initial control study is carried out in order to measure baseline receptor densities. PET scans on the monkey are separated by at least two weeks. Unlabeled compound of the invention is administered intravenously, dissolved in 80% PEG 400:40% sterile saline.

PET Data Analysis:

PET data are analyzed by using cerebellum as the reference region and using the distribution volume region (DVR) method. This method has been applied for the analysis of ¹⁸F-altanserin PET data in non-human primate and human studies (Smith *et al.*, *Synapse*, 30:380-392, (1998)).

Example 8: The Effect of Compounds of the Invention and Zolpidem on Delta Power in Rats.

In this example, the effect of compounds of the invention on sleep and wakefulness can
5 be compared to the reference drug zolpidem. Drugs are administered during the middle of the light period (inactivity period).

Briefly, compounds of the invention are tested for their effects on sleep parameters and are compared to zolpidem (5.0 mg/kg, Sigma, St. Louis, MO) and vehicle control (80% Tween 80, Sigma, St. Louis, MO). A repeated measures design is employed in which each rat is to
10 receive seven separate dosings via oral gavage. The first and seventh dosings are vehicle and the second through sixth are the test compounds and zolpidem given in counter-balanced order. Since all dosings are administered while the rats are connected to the recording apparatus, 60% CO₂/40% O₂ gas is employed for light sedation during the oral gavage process. Rats are fully recovered within 60 seconds following the procedure. A minimum of three days elapses
15 between dosings. In order to test the effect of the compounds on sleep consolidation, dosing occurs during the middle of the rats' normal inactive period (6 hours following lights on). Dosing typically occurs between 13:15 and 13:45 using a 24 hour notation. All dosing solutions are made fresh on the day of dosing. Following each dosing, animals are continuously recorded until lights out the following day (~30 hours).

20 **Animal Recording and Surgical Procedures:**

Animals are housed in a temperature controlled recording room under a 12/12 light/dark cycle (lights on at 7:00 am) and have food and water available *ad libitum*. Room temperature (24 ± 2 °C), humidity (50 ± 20% relative humidity) and lighting conditions are monitored continuously *via* computer. Drugs are administered *via* oral gavage as described above, with a
25 minimum of three days between dosings. Animals are inspected daily in accordance with NIH guidelines.

Eight male Wistar rats (300 ± 25 g; Charles River, Wilmington, MA) are prepared with chronic recording implants for continuous electroencephalograph (EEG) and electromyograph (EMG) recordings. Under isoflurane anesthesia (1–4%), the fur is shaved from the top of the
30 skull and the skin is disinfected with Betadine and alcohol. A dorsal midline incision is made, the temporalis muscle retracted and the skull cauterized and thoroughly cleaned with a 2% hydrogen peroxide solution. Stainless steel screws (#000) are implanted into the skull and serve as epidural electrodes. EEG electrodes are positioned bilaterally at +2.0 mm AP from bregma and 2.0 mm ML and at -6.0 mm AP and 3.0 mm ML. Multi-stranded twisted stainless steel wire
35 electrodes are sutured bilaterally in the neck muscles for recording of the EMG. EMG and EEG electrodes are soldered to a head plug connector that is affixed to the skull with dental acrylic. Incisions are closed with suture (silk 4-0) and antibiotics administered topically. Pain is relieved

by a long-lasting analgesic (buprenorphine) administered intramuscularly once post-operatively. Post-surgery, each animal is placed in a clean cage and observed until it is recovered. Animals are permitted a minimum of one week post-operative recovery before study.

For sleep recordings, animals are connected *via* a cable and a counter-balanced
5 commutator to a Neurodata model 15 data collection system (Grass-Telefactor, West Warwick, RI). The animals are allowed an acclimation period of at least 48 hours before the start of the experiment and are connected to the recording apparatus continuously throughout the experimental period except to replace damaged cables. The amplified EEG and EMG signals are digitized and stored on a computer using SleepSign software (Kissei Comtec, Irvine CA).

10 **Data Analysis:**

EEG and EMG data are scored visually in 10 second epochs for waking (W), REMS, NREMS. Scored data are analyzed and expressed as time spent in each state per half hour. Sleep bout length and number of bouts for each state are calculated in hourly bins. A "bout" consists of a minimum of two consecutive epochs of a given state. EEG delta power (0.5-3.5
15 Hz) within NREMS is also analyzed in hourly bins. The EEG spectra during NREMS are obtained offline with a fast Fourier transform algorithm on all epochs without artifact. The delta power is normalized to the average delta power in NREMS between 23:00 and 1:00, a time when delta power is normally lowest.

Data are analyzed using repeated measures ANOVA. Light phase and dark phase data
20 are analyzed separately. Both the treatment effect within each rat and the time by treatment effect within each rat is analyzed. Since two comparisons are made, a minimum value of $P < 0.025$ is required for *post hoc* analysis. When statistical significance is found from the ANOVAs, t-tests are performed comparing all compounds to vehicle and the test compounds to zolpidem.

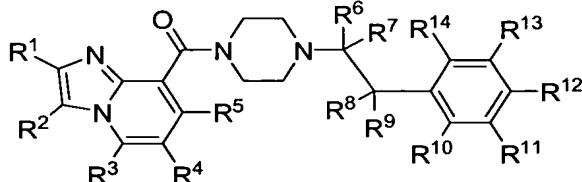
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Those skilled in the art will recognize that various modifications, additions, substitutions and variations to the illustrative examples set forth herein can be made without departing from the spirit of the invention and are, therefore, considered within the scope of the invention. All documents referenced above, including, but not limited to, printed publications
30 and provisional and regular patent applications, are incorporated herein by reference in their entirety.

What is claimed is:

1. A compound selected from compounds of Formula (Ia) and pharmaceutically acceptable salts, solvates and hydrates thereof:

5



(Ia)

wherein:

R¹, R², R³, R⁴ and R⁵ are each independently selected from the group consisting of H, C₁-C₆ acyl, C₁-C₆ acyloxy, C₁-C₆ alkoxy, C₁-C₆ alkoxycarbonylamino, C₁-C₆ alkyl, C₁-C₆ alkylamino, C₂-C₈ dialkylamino, C₁-C₆ alkylcarboxamide, C₁-C₆ alkylsulfonamide, C₁-C₆ alkylsulfinyl, C₁-C₆ alkylsulfonyl, C₁-C₆ alkylureyl, amino, aryl, aryl-C₁-C₄-alkylenyl, carbo-C₁-C₆-alkoxy, carboxamide, carboxy, cyano, C₃-C₇ cycloalkyl, C₂-C₆ dialkylcarboxamide, C₁-C₆ haloalkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkylsulfinyl, C₁-C₆ haloalkylsulfonyl, halogen, heteroaryl, heterocyclyl, hydroxyl, nitro and sulfonamide;

10

R⁶ and R⁷ are each independently selected from the group consisting of H, C₁-C₆ acyl, C₁-C₃ alkyl, aryl, carboxamide, carboxy, C₃-C₇ cycloalkyl, C₁-C₆ haloalkyl, heteroaryl and heterocyclyl;

15

20

R⁸ and R⁹ are each independently selected from the group consisting of H, C₁-C₆ acyl, C₁-C₃ alkyl, aryl, carboxamide, C₁-C₃ alkoxy, carboxy, cyano, C₃-C₇ cycloalkyl, C₁-C₃ haloalkyl, halogen and hydroxyl; or

R⁸ and R⁹ taken together form oxo; or

R⁸ and R⁹ together with the atom to which they are both bonded form a C₃-C₇ cycloalkyl ring; and

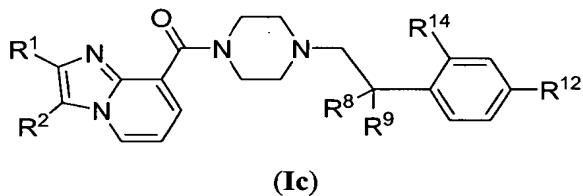
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30

R¹⁰, R¹¹, R¹², R¹³ and R¹⁴ are each independently selected from the group consisting of H, C₁-C₆ acyl, C₁-C₆ acyloxy, C₁-C₆ alkoxy, C₁-C₆ alkoxycarbonylamino, C₁-C₆ alkyl, C₁-C₆ alkylamino, C₁-C₆ alkylcarboxamide, C₁-C₆ alkylsulfinyl, C₁-C₆ alkylsulfonamide, C₁-C₆ alkylsulfonyl, C₁-C₆ alkylureyl, amino, carbo-C₁-C₆ alkoxy, carboxamide, carboxy, cyano, C₃-C₆ cycloalkyl, C₃-C₇ cycloalkylcarbonyl, C₂-C₈ dialkylamino, C₂-C₆ dialkylcarboxamide, C₁-C₆ haloalkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkylsulfinyl, C₁-C₆ haloalkylsulfonyl, halogen, heteroaryl, heterocyclyl, hydroxyl, nitro, phenyl, sulfonamide and sulfonic acid; wherein said phenyl group is optionally substituted with 1, 2 or 3 halogens.

2. The compound according to claim 1, wherein R¹ and R² are each independently selected from the group consisting of H, C₁-C₆ acyloxy, C₁-C₆ alkoxy, C₁-C₆ alkyl, C₁-C₆ alkylsulfonyl, aryl, aryl-C₁-C₄-alkylenyl, carbo-C₁-C₆ alkoxy, carboxy, cyano, C₃-C₇ cycloalkyl, C₁-C₆ haloalkoxy, C₁-C₆ haloalkyl, halogen, heteroaryl, heterocycl and hydroxyl.
- 5
3. The compound according to claim 1, wherein R¹ and R² are each independently selected from the group consisting of H, methyl, *t*-butyl, phenyl, cyano, trifluoromethyl, chloro and bromo.
- 10
4. The compound according to claim 1, wherein R¹ is H; and R² is cyano, chloro or bromo.
5. The compound according to claim 1, wherein R¹ and R² are both H.
- 15
6. The compound according to any one of claims 1 to 5, wherein R³, R⁴ and R⁵ are each independently selected from the group consisting of H, methyl, methoxy and bromo.
7. The compound according to any one of claims 1 to 5, wherein R³, R⁴ and R⁵ are each H.
- 20
8. The compound according to any one of claims 1 to 8, wherein R⁶ and R⁷ are each independently selected from the group consisting of H and methyl.
9. The compound according to any one of claims 1 to 8, wherein R⁶ and R⁷ are both H.
- 25
10. The compound according to any one of claims 1 to 11, wherein:
- R⁸ and R⁹ are each independently selected from the group consisting of H, C₁-C₃ alkyl, aryl, C₁-C₃ alkoxy, C₃-C₇ cycloalkyl, C₁-C₃ haloalkyl, halogen and hydroxyl; or
- R⁸ and R⁹ taken together form oxo; or
- 30
- R⁸ and R⁹ together with the atom to which they are both bonded form a C₃-C₇ cycloalkyl ring.
11. The compound according to any one of claims 1 to 11, wherein R⁸ and R⁹ are both H.
- 35
12. The compound according to any one of claims 1 to 11, wherein R⁸ and R⁹ together form oxo.

13. The compound according to any one of claims 1 to 12, wherein R¹⁰, R¹¹, R¹², R¹³ and R¹⁴ are each independently selected from the group consisting of H, C₁-C₆ acyloxy, C₁-C₆ alkoxy, C₁-C₆ alkyl, C₁-C₆ alkylamino, C₂-C₈ dialkylamino, C₁-C₆ alkylcarboxamide, C₁-C₆ alkylsulfonamide, C₁-C₆ alkylsulfonyl, amino, carboxamide, carboxy, cyano, C₃-C₆ cycloalkyl, C₂-C₆ dialkylcarboxamide, C₁-C₆ haloalkoxy, C₁-C₆ haloalkyl, halogen, heteroaryl, heterocycl, hydroxyl, nitro, phenyl, sulfonamide and sulfonic acid; 5 wherein said phenyl group is optionally substituted with 1, 2 or 3 halogens.
14. The compound according to any one of claims 1 to 12, wherein R¹⁰, R¹¹, R¹², R¹³ and R¹⁴ are each independently selected from the group consisting of H, methyl, methoxy, dimethylamino, -NHSO₂CH₃, methylsulfonyl, carboxamide, carboxy, cyano, cyclohexyl, fluoro, chloro, trifluoromethoxy, difluoromethoxy, trifluoromethyl, morpholin-4-yl, pyrrolidin-1-yl, thien-2-yl, hydroxyl, nitro, phenyl and sulfonic acid. 10
15. The compound according to any one of claims 1 to 12, wherein:
- R¹⁰ and R¹² are both F; and
- R¹¹, R¹³ and R¹⁴ are each H.
16. The compound according to claim 1, selected from compounds of Formula (**Ic**) and pharmaceutically acceptable salts, solvates or hydrates thereof. 20
- (Ic)**
- wherein:
- R¹ is selected from the group consisting of H, C₁-C₆ alkyl, aryl and C₁-C₆ haloalkyl; 25
- R² is selected from the group consisting of H, cyano and halogen;
- R⁸ and R⁹ are each independently selected from the group consisting of H and halogen; or
- R⁸ and R⁹ together form oxo; and
- R¹² and R¹⁴ are each independently selected from the group consisting of H and halogen. 30
17. The compound according to claim 1, selected from compounds of Formula (**Ic**) and pharmaceutically acceptable salts, solvates or hydrates thereof:



wherein:

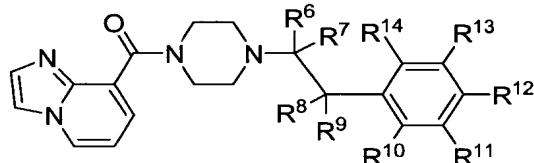
5 R¹ is selected from the group consisting of H, methyl, *t*-butyl, phenyl and trifluoromethyl;

R² is selected from the group consisting of H, cyano, chloro and bromo;

R⁸ and R⁹ are each independently selected from the group consisting of H and F; or R⁸ and R⁹ together form oxo; and

10 R¹² and R¹⁴ are each independently selected from the group consisting of H, fluoro and chloro.

18. The compound according to claim 1, selected from compounds of Formula (Ie) and pharmaceutically acceptable salts, solvates or hydrates thereof:



15 wherein:

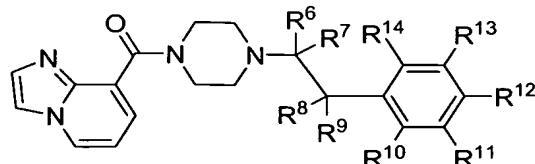
R⁶ and R⁷ are each independently selected from the group consisting of H and C₁-C₃ alkyl;

20 R⁸ and R⁹ are each independently selected from the group consisting of H and halogen; or

R⁸ and R⁹ together form oxo; and

25 R¹⁰, R¹¹, R¹², R¹³ and R¹⁴ are each independently selected from the group consisting of H, C₁-C₆ alkoxy, C₁-C₆ alkyl, C₂-C₈ dialkylamino, C₁-C₆ alkylsulfonamide, C₁-C₆ alkylsulfonyl, carboxamide, carboxy, cyano, C₃-C₆ cycloalkyl, C₁-C₆ haloalkoxy, C₁-C₆ haloalkyl, heteroaryl, halogen, heterocyclyl, hydroxyl, nitro, phenyl and sulfonic acid.

19. The compound according to claim 1, selected from compounds of Formula (Ie) and pharmaceutically acceptable salts, solvates or hydrates thereof:



(Ie)

wherein:

R⁶ and R⁷ are both H;

5 R⁸ and R⁹ are each independently selected from the group consisting of H and F; or

R⁸ and R⁹ together form oxo; and

10 R¹⁰, R¹¹, R¹², R¹³ and R¹⁴ are each independently selected from the group consisting of H, methyl, methoxy, dimethylamino, -NHSO₂CH₃, methylsulfonyl, carboxamide, carboxy, cyano, cyclohexyl, fluoro, chloro, trifluoromethoxy, difluoromethoxy, trifluoromethyl, morpholin-4-yl, pyrrolidin-1-yl, thien-2-yl, hydroxyl, nitro, phenyl and sulfonic acid.

20. The compound according to claim 1 selected from the following compounds and
15 pharmaceutically acceptable salts, solvates or hydrates thereof:

(3-bromoimidazo[1,2-*a*]pyridin-8-yl)(4-(2,4-difluorophenethyl)piperazin-1-yl)methanone;

8-(4-(2,4-difluorophenethyl)piperazine-1-carbonyl)imidazo[1,2-*a*]pyridine-3-carbonitrile;

20 (4-(2,4-difluorophenethyl)piperazin-1-yl)(imidazo[1,2-*a*]pyridin-8-yl)methanone;

1-(4-fluorophenyl)-2-(4-(imidazo[1,2-*a*]pyridine-8-carbonyl)piperazin-1-yl)ethanone;

(4-(4-fluorophenethyl)piperazin-1-yl)(imidazo[1,2-*a*]pyridin-8-yl)methanone;

25 (4-(4-fluorophenethyl)piperazin-1-yl)(2-(trifluoromethyl)imidazo[1,2-*a*]pyridin-8-yl)methanone;

(2-*tert*-butylimidazo[1,2-*a*]pyridin-8-yl)(4-(4-fluorophenethyl)piperazin-1-yl)methanone;

(4-(4-fluorophenethyl)piperazin-1-yl)(2-methylimidazo[1,2-*a*]pyridin-8-yl)methanone;

30 (4-(4-fluorophenethyl)piperazin-1-yl)(2-phenylimidazo[1,2-*a*]pyridin-8-yl)methanone;

(4-(2-fluoro-2-(4-fluorophenyl)ethyl)piperazin-1-yl)(imidazo[1,2-*a*]pyridin-8-yl)methanone;

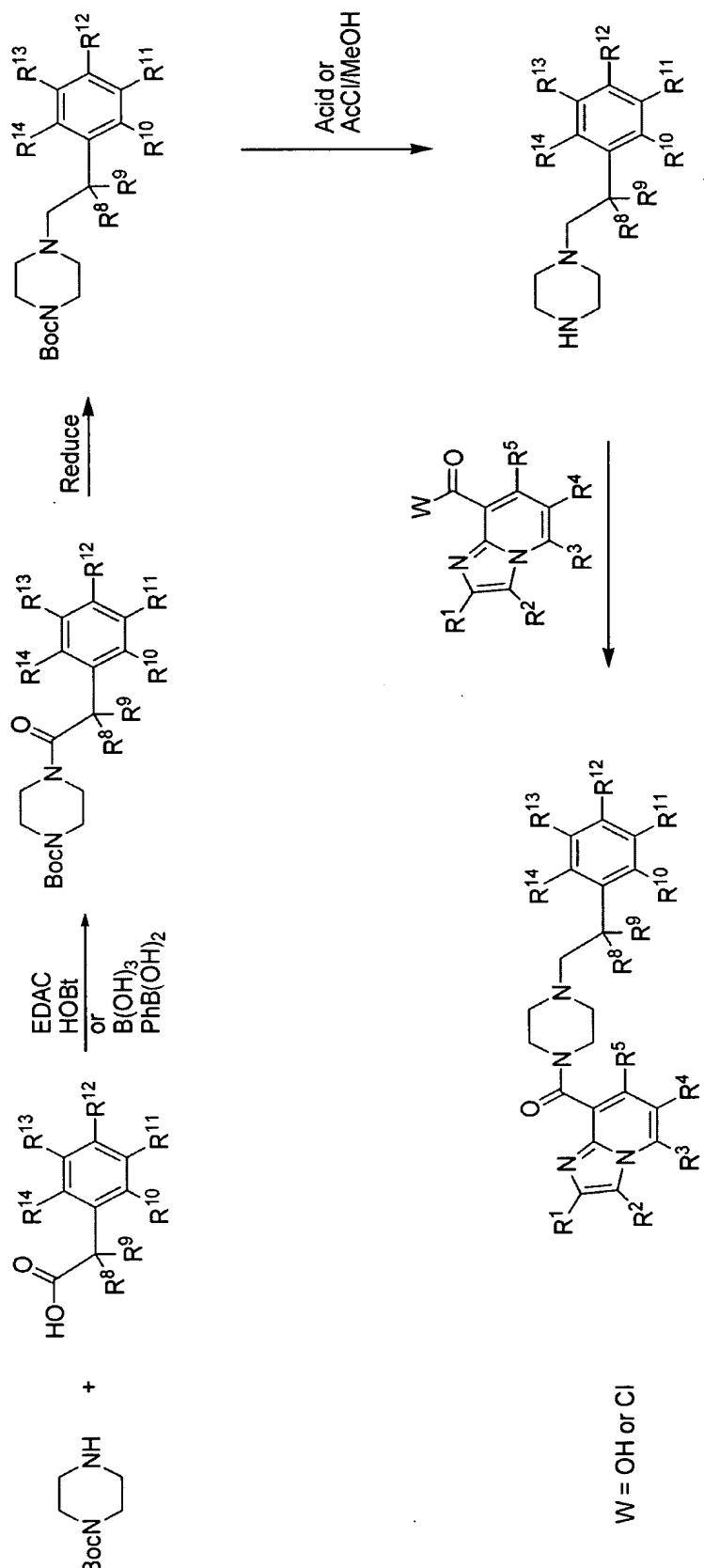
(3-chloroimidazo[1,2-*a*]pyridin-8-yl)(4-(2,4-difluorophenethyl)piperazin-1-yl)methanone;
imidazo[1,2-*a*]pyridin-8-yl(4-(4-methoxyphenethyl)piperazin-1-yl)methanone;
(4-(3,4-dimethoxyphenethyl)piperazin-1-yl)(imidazo[1,2-*a*]pyridin-8-
5
yl)methanone;
(4-(3-fluorophenethyl)piperazin-1-yl)(imidazo[1,2-*a*]pyridin-8-yl)methanone;
(4-(4-chlorophenethyl)piperazin-1-yl)(imidazo[1,2-*a*]pyridin-8-yl)methanone;
(4-(3-chlorophenethyl)piperazin-1-yl)(imidazo[1,2-*a*]pyridin-8-yl)methanone;
(4-(2-chlorophenethyl)piperazin-1-yl)(imidazo[1,2-*a*]pyridin-8-yl)methanone;
10
(4-(2-fluorophenethyl)piperazin-1-yl)(imidazo[1,2-*a*]pyridin-8-yl)methanone;
(4-(2,4-dichlorophenethyl)piperazin-1-yl)(imidazo[1,2-*a*]pyridin-8-
yl)methanone;
15
1-(2,4-difluorophenyl)-2-(4-(imidazo[1,2-*a*]pyridine-8-carbonyl)piperazin-1-
yl)ethanone;
2-(4-(imidazo[1,2-*a*]pyridine-8-carbonyl)piperazin-1-yl)-1-(4-(pyrrolidin-1-
yl)phenyl)ethanone;
20
2-(4-(imidazo[1,2-*a*]pyridine-8-carbonyl)piperazin-1-yl)-1-(4-(trifluoromethoxy)phenyl)ethanone;
N-(2-hydroxy-5-(2-(4-(imidazo[1,2-*a*]pyridine-8-carbonyl)piperazin-1-
yl)acetyl)phenyl)methanesulfonamide;
1-(2-chloro-5-(trifluoromethyl)phenyl)-2-(4-(imidazo[1,2-*a*]pyridine-8-
carbonyl)piperazin-1-yl)ethanone;
1-(biphenyl-4-yl)-2-(4-(imidazo[1,2-*a*]pyridine-8-carbonyl)piperazin-1-
yl)ethanone;
25
2-(4-(imidazo[1,2-*a*]pyridine-8-carbonyl)piperazin-1-yl)-1-(4-(methylsulfonyl)phenyl)ethanone;
(4-(2,4-difluorophenethyl)piperazin-1-yl)(5,7-dimethylimidazo[1,2-*a*]pyridin-8-
yl)methanone;
30
1-(4-cyclohexylphenyl)-2-(4-(imidazo[1,2-*a*]pyridine-8-carbonyl)piperazin-1-
yl)ethanone;
1-(4-(difluoromethoxy)phenyl)-2-(4-(imidazo[1,2-*a*]pyridine-8-
carbonyl)piperazin-1-yl)ethanone;
2-(4-(imidazo[1,2-*a*]pyridine-8-carbonyl)piperazin-1-yl)-1-phenylpropan-1-one;
1-(4-chloro-2-fluoro-5-methylphenyl)-2-(4-(imidazo[1,2-*a*]pyridine-8-
35
carbonyl)piperazin-1-yl)ethanone;
1-(5-chloro-2-methoxy-4-methylphenyl)-2-(4-(imidazo[1,2-*a*]pyridine-8-
carbonyl)piperazin-1-yl)ethanone;

- 1-(3,5-bis(trifluoromethyl)phenyl)-2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)ethanone;
- 2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)-1-(4-(trifluoromethyl)phenyl)ethanone;
- 5 2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)-1-(4-(thiophen-2-yl)phenyl)ethanone;
- (4-(2,4-difluorophenethyl)piperazin-1-yl)(7-methoxyimidazo[1,2-a]pyridin-8-yl)methanone;
- 10 2-hydroxy-5-(2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)acetyl)benzamide;
- 2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)-1-(2-(trifluoromethyl)phenyl)ethanone;
- 15 4-(2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)acetyl)benzonitrile;
- 1-(4-hydroxyphenyl)-2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)ethanone;
- 1-(4-(dimethylamino)phenyl)-2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)ethanone;
- 20 1-(5-chloro-2-methoxy-4-methyl-3-nitrophenyl)-2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)ethanone;
- 2-(4-(imidazo[1,2-a]pyridine-8-carbonyl)piperazin-1-yl)-1-(4-morpholinophenyl)ethanone; and
- (6-bromoimidazo[1,2-a]pyridin-8-yl)(4-(2,4-difluorophenethyl)piperazin-1-yl)methanone.
- 25 21. A pharmaceutical composition comprising a compound according to any one of claims 1 to 20 and a pharmaceutically acceptable carrier.
22. A method for treating a 5-HT_{2A} mediated disorder in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 20 or a pharmaceutical composition according to claim 21.
- 30 23. The method according to claim 22, wherein said 5-HT_{2A} mediated disorder is a sleep disorder.
- 35 24. The method according to claim 23, wherein said sleep disorder is a dyssomnia.

25. The method according to claim 23, wherein said sleep disorder is insomnia.
26. The method according to claim 23, wherein said sleep disorder is a parasomnia.
- 5 27. A method for increasing slow wave sleep in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 20 or a pharmaceutical composition according to claim 21.
- 10 28. A method for improving sleep consolidation in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 20 or a pharmaceutical composition according to claim 21.
- 15 29. A method for improving sleep maintenance in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 20 or a pharmaceutical composition according to claim 21.
- 20 30. A method for treating a condition associated with platelet aggregation in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 20 or a pharmaceutical composition according to claim 21.
- 25 31. Use of a compound according to any one of claims 1 to 20 in the manufacture of a medicament for the treatment of a 5-HT_{2A} mediated disorder.
32. Use of a compound according to any one of claims 1 to 20 in the manufacture of a medicament for the treatment of a sleep disorder.
- 30 33. Use of a compound according to any one of claims 1 to 20 in the manufacture of a medicament for the treatment of a dyssomnia.
34. Use of a compound according to any one of claims 1 to 20 in the manufacture of a medicament for the treatment of insomnia.

35. Use of a compound according to any one of claims 1 to 20 in the manufacture of a medicament for the treatment of a parasomnia.
36. Use of a compound according to any one of claims 1 to 20 in the manufacture of a medicament for increasing slow wave sleep.
5
37. Use of a compound according to any one of claims 1 to 20 in the manufacture of a medicament for improving sleep consolidation.
- 10 38. Use of a compound according to any one of claims 1 to 20 in the manufacture of a medicament for improving sleep maintenance.
39. Use of a compound according to any one of claims 1 to 20 in the manufacture of a medicament for the treatment of a condition associated with platelet aggregation.
15
40. A compound according to any one of claims 1 to 20 for use in a method of treatment of the human or animal body by therapy.
41. A compound according to any one of claims 1 to 20 for use in a method for the treatment of a 5-HT_{2A} mediated disorder.
20
42. A compound according to any one of claims 1 to 20 for use in a method for the treatment of a sleep disorder.
- 25 43. A compound according to any one of claims 1 to 20 for use in a method for the treatment of a dyssomnia.
44. A compound according to any one of claims 1 to 20 for use in a method for the treatment of insomnia.
30
45. A compound according to any one of claims 1 to 20 for use in a method for the treatment of a parasomnia.
46. A compound according to any one of claims 1 to 20 for use in a method for increasing slow wave sleep.
35

47. A compound according to any one of claims 1 to 20 for use in a method for improving sleep consolidation.
48. A compound according to any one of claims 1 to 20 for use in a method for improving sleep maintenance.
5
49. A compound according to any one of claims 1 to 20 for use in a method for the treatment of a condition associated with platelet aggregation.
- 10 50. A process for preparing a composition comprising admixing a compound according to any one of claims 1 to 20 and a pharmaceutically acceptable carrier.

**Figure 1**

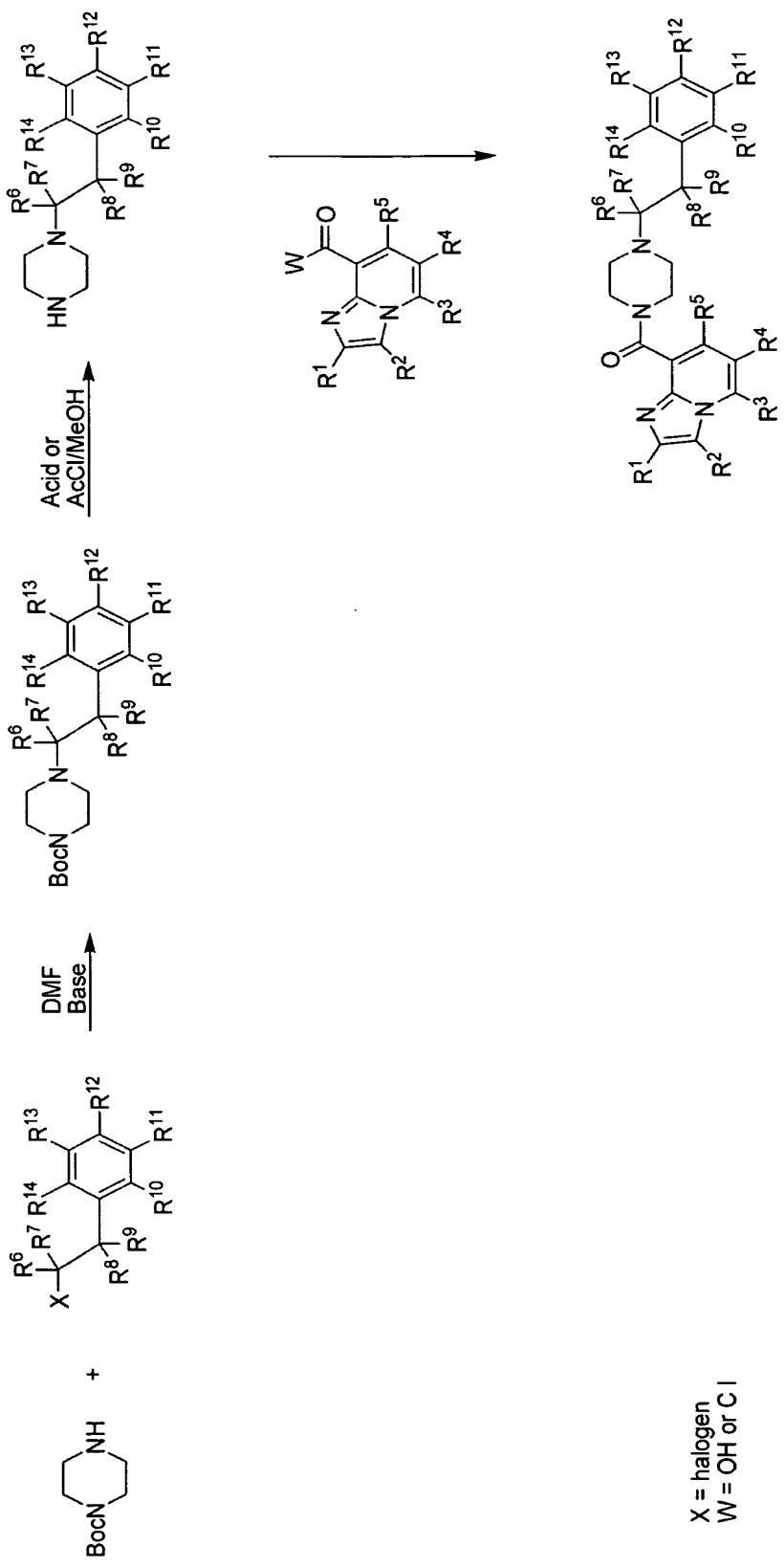
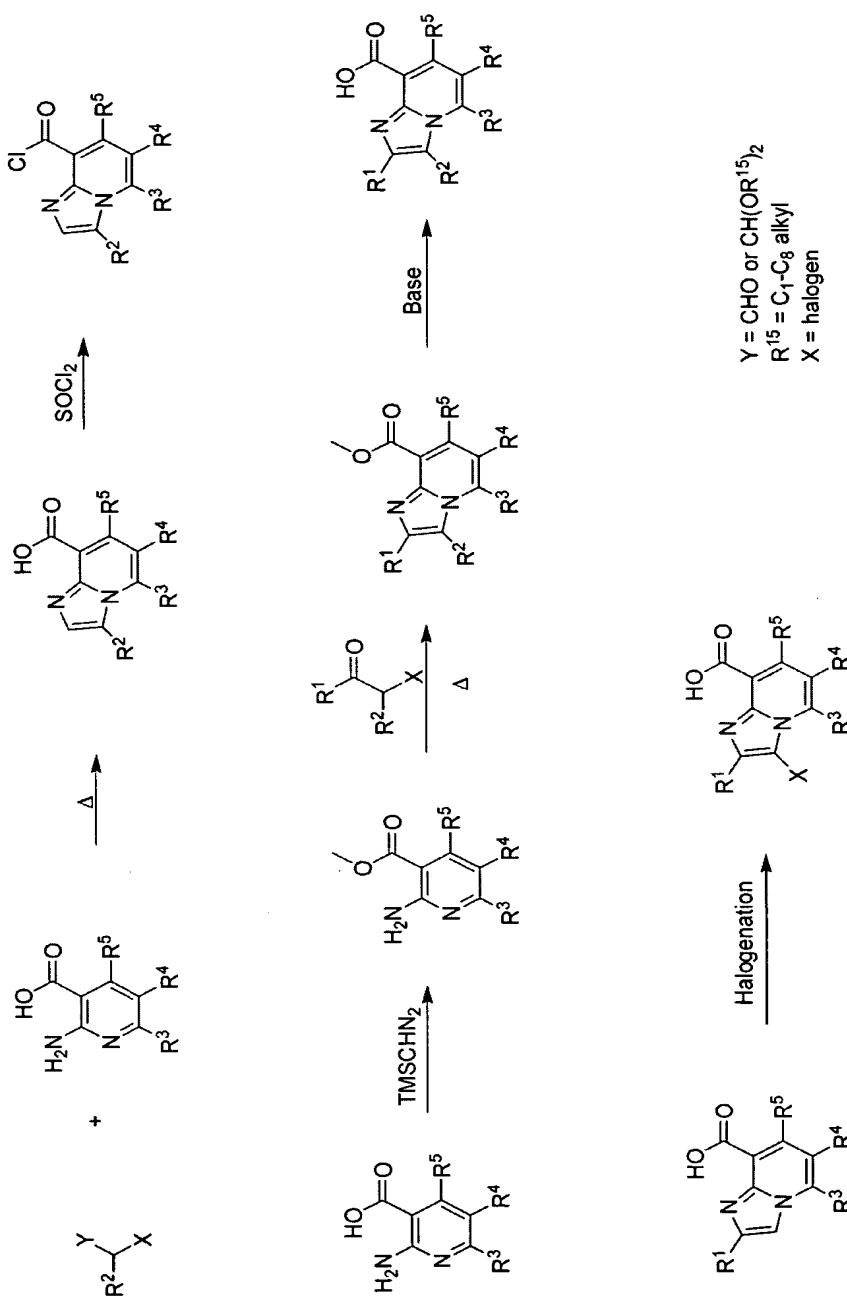
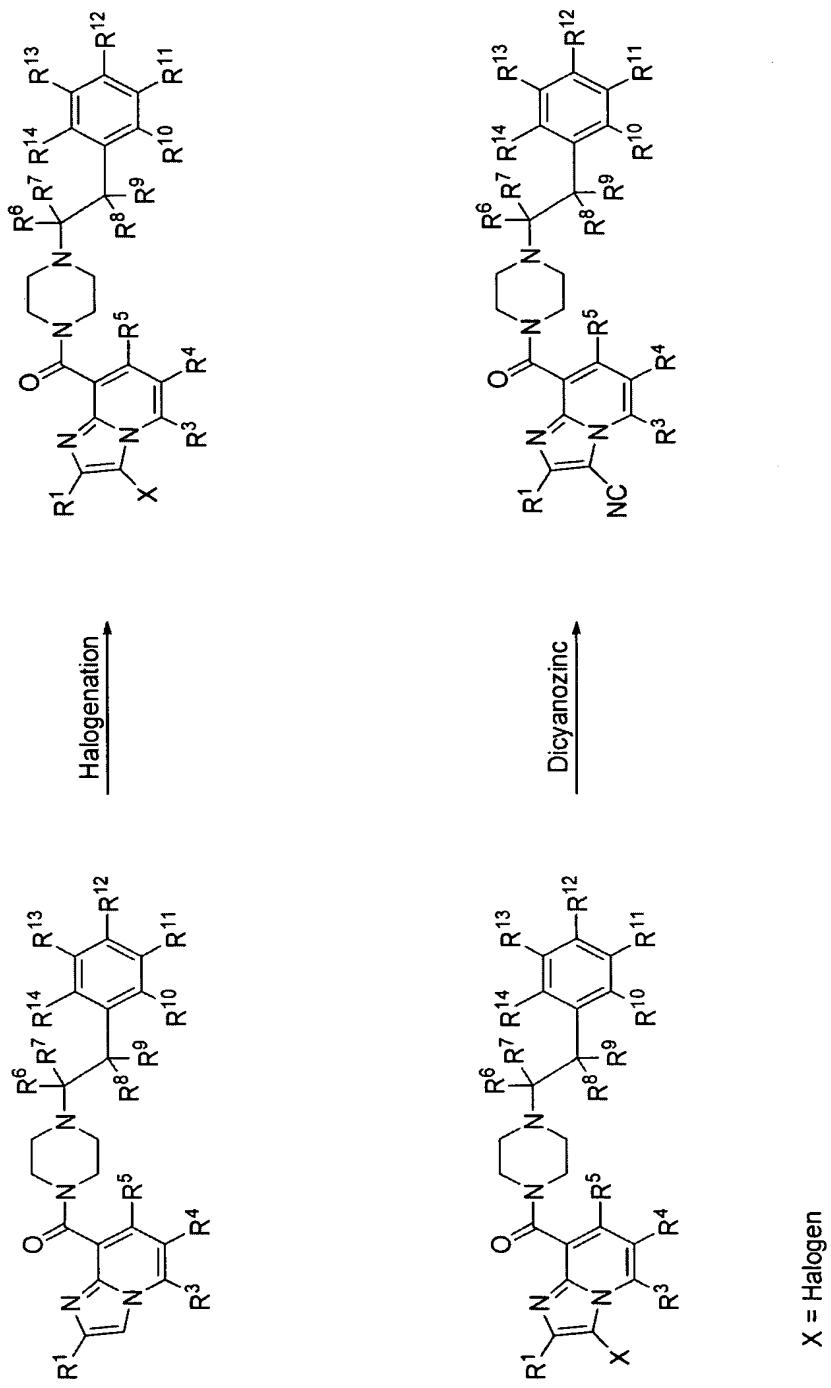


Figure 2

**Figure 3**

**Figure 4**

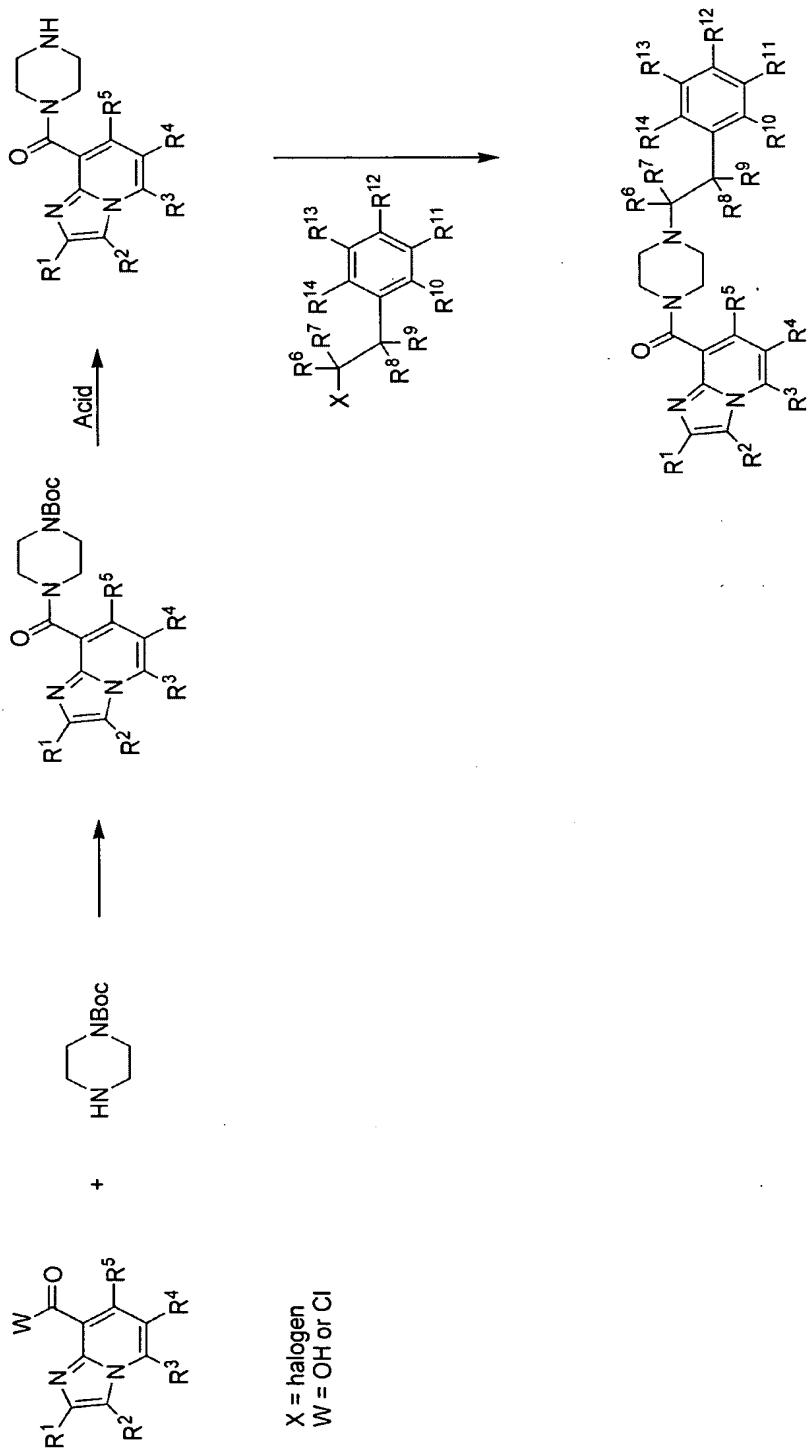
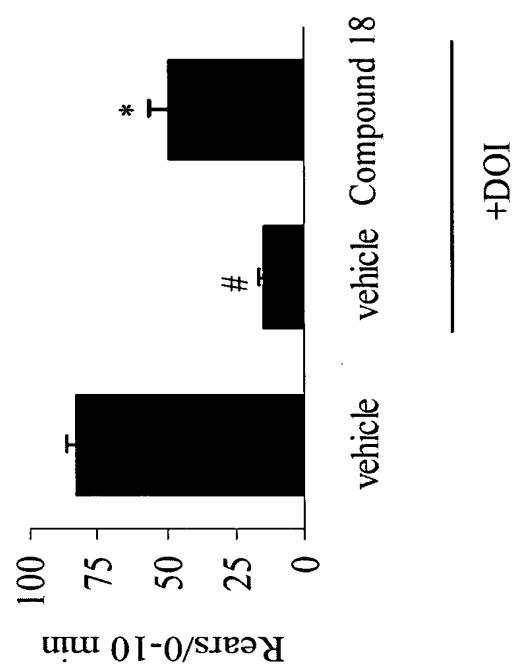


Figure 5

Attenuation of DOI-induced hypolocomotion in rats

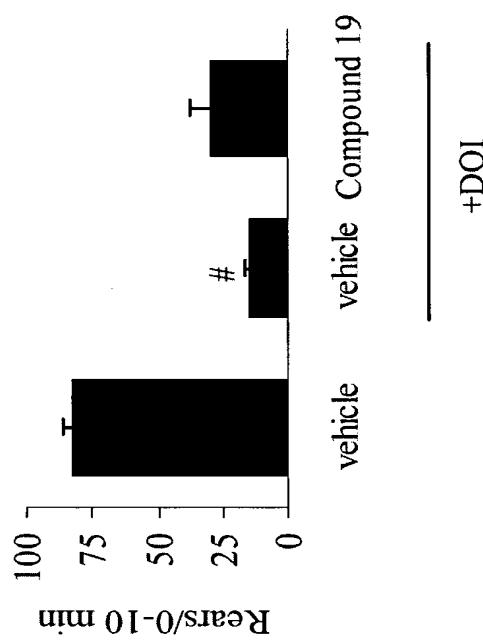


P<0.01 vs. vehicle/saline

*P<0.01 vs. vehicle/DOI

Figure 6

Attenuation of DOI-induced hypolocomotion in rats



P<0.01 vs. vehicle/saline

Figure 7

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(54) Title: IMIDAZO[1,2- α]PYRIDINE DERIVATIVES AS MODULATORS OF THE 5-HT_{2A} SEROTONIN RECEPTOR USEFUL FOR THE TREATMENT OF DISORDERS RELATED THERETO

(57) Abstract: Imidazo[1,2- α]pyridine derivatives of Formula (Ia) and pharmaceutical compositions thereof that modulate the activity of the 5-HT_{2A} serotonin receptor. Compounds and pharmaceutical compositions thereof are directed to methods useful in the treatment of insomnia, dyssomnia, parasomnia and related sleep disorders, platelet aggregation, coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, thrombosis, asthma or symptoms thereof, agitation or symptoms thereof, behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorders, psychosis, acute schizophrenia, chronic schizophrenia, NOS schizophrenia and related disorders, diabetic- related disorders, progressive multifocal leukoencephalopathy and the like. The present invention also relates to methods for the treatment of 5-HT_{2A} serotonin receptor mediated disorders in combination with other pharmaceutical agents administered separately or together.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/009740

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/437 A61P25/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2006/086705 A (AVENTIS PHARMA INC [US]; FINK DAVID MARK [US]; SMITH HELEN KATHERINE ()) 17 August 2006 (2006-08-17) claim 1; table 17 -----	1-50
A	WO 2005/021545 A (BIOVITRUM AB [SE]; BERTHOLD MALIN [SE]; CROSSLEY ROGER [GB]; WARD TERR) 10 March 2005 (2005-03-10) page 36; claim 1 -----	1-50
A	US 2007/043058 A1 (BANG-ANDERSEN BENNY [DK] ET AL) 22 February 2007 (2007-02-22) paragraph [0002]; claim 1 -----	1-50



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

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